Radiation Assurance

Roll-out Phase Two Evaluation

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1.0 Executive summary

As part of the Health Research Authority's (HRA's) commitment to improve and streamlining research in England, it was identified that radiation aspects of new studies were causing delays in site set-up. Difficulties in finding appropriate experts to undertake the review, as well as issues not just with the quality of information provided within research protocols, but also within the expert reviews authorised by the Lead Medical Physics Expert (MPE) and Lead Clinical Radiation Expert (CRE) in the Integrated Research Application Form (IRAS) together with differing payment frameworks for the completion of these authorisations, led the HRA to pilot the Streamlining Radiation Review – Medical Exposure Project in collaboration with the Experimental Cancer Medicines Centres (ECMCs) and Cancer Research UK (CRUK).

The pilot ran from January to October 2015, during which time a total of 16 studies were processed.

The evaluation of the aforementioned project highlighted the need for using MPE and CRE experts based across a number of organisations to complete the technical authorisations. It also revealed the key to a complete authorisation, with all the necessary details to enable site set up, and the timescales by which the reviews could be undertaken, were dependent on the sponsor/sponsor representatives providing all the relevant information (which may have previously been omitted or unclear in the protocol) at submission stage.

Following completion of the pilot, the HRA continued to build upon the Streamlining Radiation Review – Medical Exposure Project pilot in order to develop and operationalise Radiation Assurance.

Originally an England only process with expert reviewers available from all UK nations, and one formal route for gaining authorisations, the project has developed with support from the Devolved Administrations, via the Four Nations Radiation Assurance Working Party[1], and is now a UK wide process with multiple routes for gaining authorisations and a bank of registered expert reviewers available from across the UK.

2.0 Introduction

The HRA, in conjunction with the Devolved Administrations, launched the new Radiation Assurance process to accept all oncology studies taking place in the NHS, on 16 April 2018.

HRA Radiation Assurance received its first study submission on 10 May 2018.

[1] The Four Nations Radiation Assurance Working Party was formalised in June 2017 and comprised of MPE/CRE representation from across the Devolved Administrations (each with links to policy leads, professional bodies/committees) and a member of the Administration of Radioactive Substances Advisory Committee (ARSAC) secretariat to ensure the process was aligned. The remit of the working party is to provide expert input/advice into the process and guidance documentation as produced by the HRA Technical Assurance (TA) team.

An evaluation of the success of Phase 1 of Radiation Assurance took into account recruitment, metrics and feedback received, this led to amendments to guidance/supporting documentation as well as reviewer training, to ensure the process remained true to its aim ahead of opening to Phase 2 of Radiation Assurance.

Phase 2 was opened on Monday 12 November. Studies with the following clinical specialisms will now be reviewed through Radiation Assurance:

- Cardiology;
- Neurology;
- Oncology;
- Rheumatology.

3.0 Current Status of Radiation Assurance – Phase Two

3.1 Reviewer recruitment

Ahead of each phase of roll out, a targeted recruitment drive is instigated, to raise awareness of the acceptance of new studies through Radiation Assurance.

Reviewer recruitment for Phase 2 of roll out opened on 17 September 2018 to CREs with clinical expertise in cardiology, neurology or rheumatology studies, and MPEs with expertise in the modalities of radiology, nuclear medicine and radiotherapy. We also continued to recruit experts with an oncology (paediatric and adult) specialism.

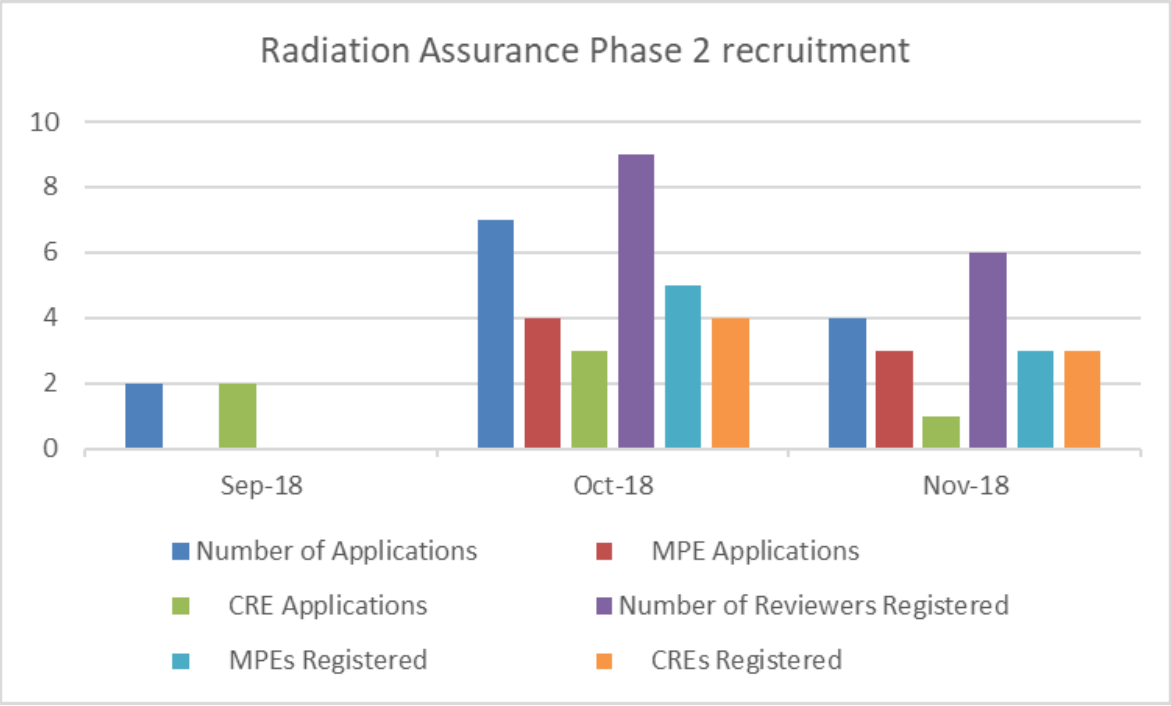

Figure 1: Graph of the number of CRE and MPE applications received by month, together with the number of reviewers registered during active recruitment for Phase 2 of roll out.

Prior to roll out of Radiation Assurance work was undertaken to ascertain the numbers of reviewers required for each phase of rollout, to ensure there are enough Reviewers and range of specialities to provide a robust service, this was based upon

information as suggested by the Evaluations and analysis of April 2014 – March 2015 data.

The number of Reviewers required for Phase 2 of Radiation Assurance, was 30 CREs and 30 MPES. Table 1 indicates that recruitment figures were well below what was required for Phase 2, however as overall recruitment had been successful (135 reviewer in total), and study submission numbers were only at 17% of total submissions, it was agreed that reviewer numbers were at an adequate level to enable Radiation Assurance to proceed with roll out.

3.1.2 Number of applications received

The highest number of applications was received from MPEs, which reflects that they are easier to communicate with than CREs. CREs are often spread out in hospitals and have different Royal Colleges with whom they can seek membership due to the wide range of clinical specialisms, whereas MPEs have far fewer professional bodies and are often employed in a single trust/health board department.

	Total
Number of Applications	13
MPE	7
CRE	6
Number of Reviewers Registered	15
MPE	8
CRE	7

Table 1: Number of reviewer applications received versus the number of reviewers registered from 17 September to 16 November 2018.

Applications were mainly received from reviewers in England, with 11 applicants from England, one from Northern Ireland and one from Wales. No CREs or MPEs from Scotland applied during this recruitment drive. The Devolved Administrations continue to be kept updated with information regarding reviewer applications in their respective nations.

Most reviewers have registered to review both HRA-managed and self-managed studies, with some reviewing only self-managed studies and a very small minority only reviewing HRA-managed studies. This is unsurprising given that studies need to meet three criteria in order to be self-managed and therefore it is anticipated that most will be HRA-managed, though self-management of studies could be an important option in particular for smaller NHS/HSC organisations.

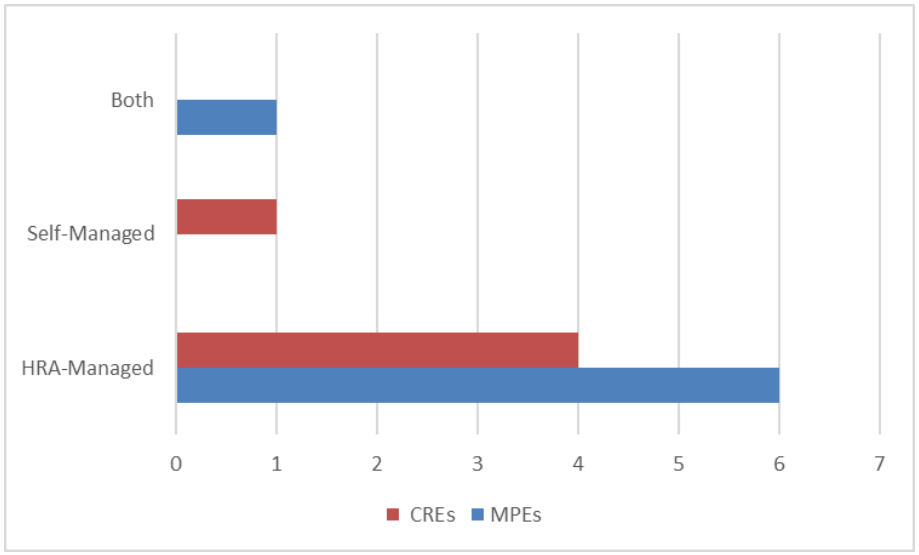

Figure 2: Split of reviewers registering by review type.

3.1.3 Reviewer expertise

Most reviewers cover just one modality (method of delivering radiation), though some reviewers are able to review studies with multiple modalities.

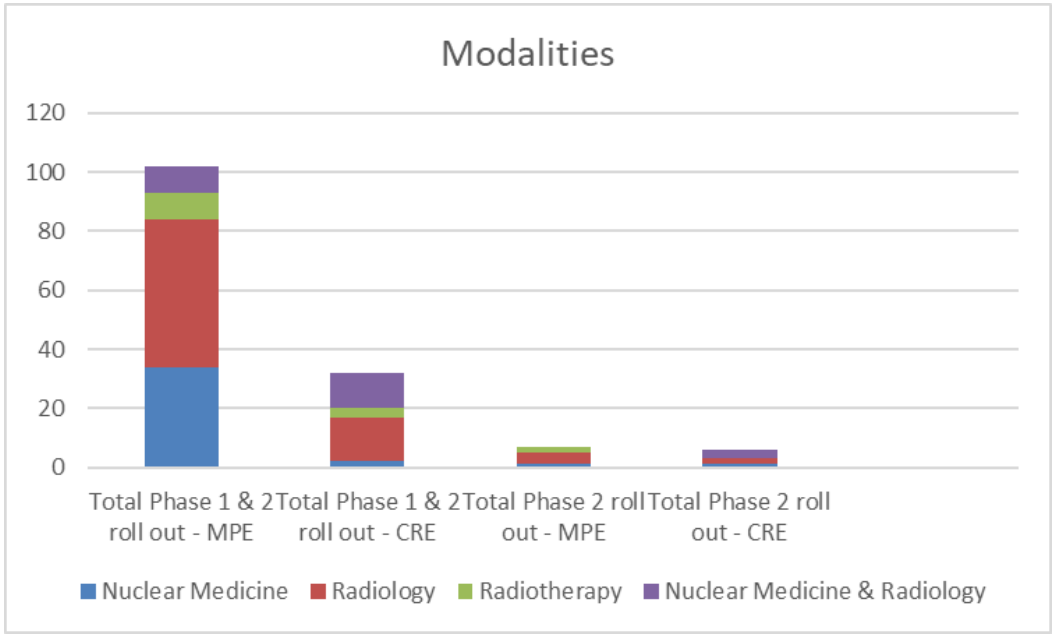

Figure 3: Pie chart of the modalities which CRE and MPE applicants are able to review.

Whilst CREs specifically with clinical knowledge of cardiology, neurology, rheumatology and adult and/or paediatric oncology were recruited, some applicants had knowledge of other clinical areas (such as gastroenterology, urology and renal) which will be useful when additional study types are accepted.

3.2 Metrics

3.2.1Study Submissions

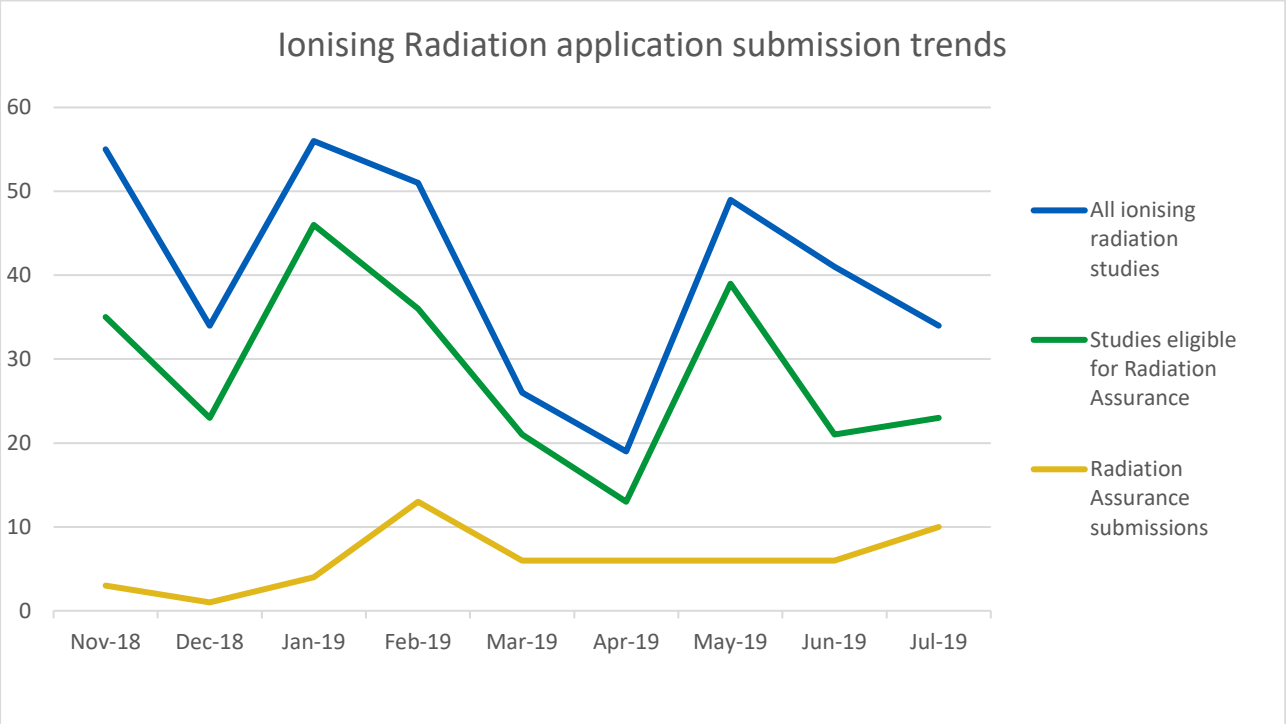

Figure 4: Submissions to Radiation Assurance as a comparison to eligible and overall study submission to the HRA.

From 12 November 2018 to 31 July 2019 a total of 257 studies which met the criteria for submission to Radiation Assurance were booked for REC review. It can be surmised that although these studies had already received their MPE and CRE authorisations in the IRAS form and therefore not all would have been able to go through Radiation Assurance due to timing, a similar number would have been able to be submitted through the process during this time frame.

During phase two of roll-out a total of 53 studies were submitted for review through Radiation Assurance, with the first submission being made 10 calendar days after the launch of phase two. This is a significant improvement on the speed of new phase submissions compared with phase one, which may be down to applicants having read and understood the submissions guidance which had previously not been published until the day of phase one roll-out (16 April 2018) which may have led to a delay in the first submission being received.

Of the 59 submissions received, 56 were reviewed as HRA-managed submissions, with the remaining 3 opting to progress through the Self-managed route. 52 studies and amendments had submitted with the required document set as specified in the submission criteria section of the Radiation Assurance webpages and IRAS help. The Technical Assurance (TA) team has invested significant time and resources in improving the information available to applicants on the process, routes to submission and required submission documents. This alongside presentations/talks with applicants/stakeholders on what makes a good submission, has helped with sponsors knowing what is required up front.

During the evaluation period, two studies were rejected, one because there was no NHS involvement and one because there was no appropriate CRE specialist available due to the clinical specialism being outside of those accepted for review. Two further studies were submitted for review and the review cancelled part way through, as the sponsors sought review outside of the process.

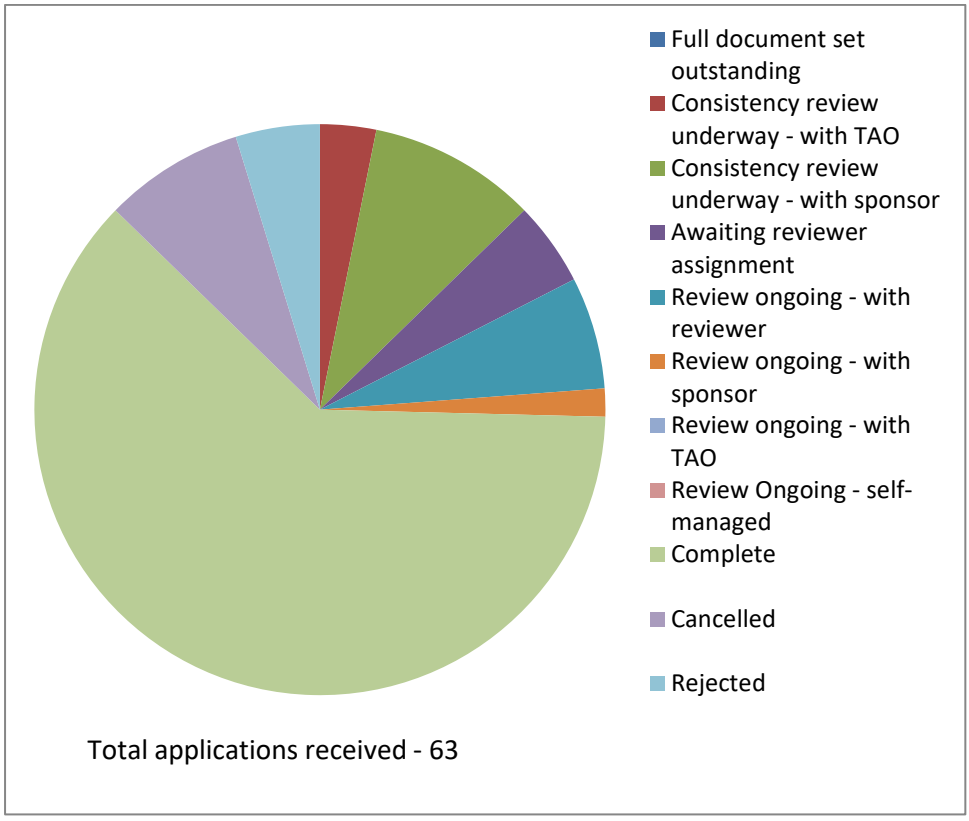

Figure 5: The status of all studies submitted during phase two roll-out as of 31 July 2019
*TAO = Technical Assurance Officer at the HRA

It should therefore be considered when reading this section that not all studies have completed the review process, and the median timelines given will not always be for the full number of studies submitted.

Full document set outstanding - with sponsor	0
Validation underway - with HRA	2
Validation underway - with sponsor	6
Awaiting reviewer assignment - with HRA	4
Review ongoing - with reviewer	4
Review ongoing - with sponsor	1
Review ongoing - with HRA	0

Table 2: The status of all open studies in phase two roll-out as of 31 July 2019, including showing which party is responsible for completing any outstanding actions.

3.2.2 Total review timeline

A total review timeline of 40 days was tested in phase one, which was from the date of submission of a full document set[2] up to the date on which confirmation of Radiation Assurance was sent by email to the sponsor. As this was being achieved in phase one, no adjustments were made prior to launch of Phase 2. Timelines achieved for this period of roll out, for HRA-managed studies ranged from 10 to 64 days.

	Mean timeline	Median timeline
Total Review Timeline	53	45
Total Review Timeline not including time with applicant	**32**	**27**
Time spent with applicant	21	13

Table 3: Total review timelines achieved during phase two of roll-out, which are from the date of submission of a full document set to the date on which the email is sent to the applicant to confirm that Radiation Assurance is in place. The figures in bold are for ease of comparison against the published timeline of 40 days.

Whilst the timeline is being met it should be considered that only approximately 21% of eligible studies were submitted for review. Any increase in the rate of submissions should be carefully monitored to assess the impact on the timelines achieved.

3.2.3 Consistency review

Consistency review was previously termed “validation” during phase one of roll-out, but this was amended at phase two to prevent any confusion or link between Radiation Assurance and REC processes. We are currently testing a 14-day consistency review timeline which is from the date of submission of a full document set up to the date on which the sponsor is informed that the application had met the consistency review criteria, excluding the time it took for the sponsor to respond to any queries.

	Mean timeline	Median timeline
Consistency Review Timeline	25	17
Consistency Review Timeline not including time with sponsor	**8**	**7**
Time spent with applicant	17	10

Table 4: Consistency review timelines (HRA-managed studies only) achieved during phase two of roll-out. This data is available for the 10 studies which have been checked for consistency through Radiation Assurance. The figures in bold are for ease of comparison against the published timeline of 14 days.

Consistency review timelines ranged from 1 to 25 days.

It should be noted that despite improved guidance available of what constitutes a research exposure and improved communications of the requirements for submission, it was not evident to some applicants completing F1 of the research

[2] A full document set is classified as the draft IRAS form, research exposure form, protocol, and any participant information sheet(s) and consent form(s) required for the study.

exposure form (REF) which exposures were radiology, nuclear medicine, radiotherapy or non-ionising and where those procedures were above standard of care. This has again resulted in the TAOs supporting those individuals to identify and categorise these exposures. It has also led to an increase in queries going to the Four-Nations Radiation Assurance Working Party where disagreement occurs regarding when a procedure becomes a research exposure versus a standard of care procedure. The aforementioned guidance has been publicised, but it may be necessary to support this with additional training and webinars that applicants can access.

As above, whilst the timelines are currently being met these will continue to be monitored carefully to ensure that applicants are being given accurate information about how long this part of the process takes, particularly for self-managed studies as this review process only measures one of the two timelines we externally publicise.

3.2.4 Sourcing reviewers

As more studies have been received through the process, it has proved challenging at times to identify reviewers who can cover multiple modalities/specialisms. This is due in part to existing workload, sickness absence and annual leave. Although reviewers have always managed to be sourced, it has meant on occasion that rather than use one reviewer to cover 2 modalities/specialties, we have had to utilise multiple reviewers in order to conduct the review. This has led to an increase in time taken to find the reviewers and an increased cost for the sponsor. Where this occurs, sponsors are kept informed and notified of any increased cost prior to proceeding.

It has been suggested through direct feedback that when contacting reviewers to ascertain whether they are able to undertake a review, it may be useful to include the level of imaging involved as this may influence the time taken to conduct the review. This was reviewed and discussed with our registered reviewers who, as a majority, felt that the initial study request email was already lengthy and as a copy of the REF with this information was attached to this email it would be a duplication of effort. The consensus amongst reviewers was that it would be more beneficial for the HRA to flag the request for review emails as ‘high importance’, to support reviewers in identifying the request for review email and enabling them to respond in the requisite time frame.

To date we have been unable to accommodate one review due to it being outside the scope of roll out. Where applicants indicate to us that they have used specific MPEs/CREs previously, we have encouraged those individuals to discuss registration through Radiation Assurance with the specific experts. Ahead of roll out to Phase three it is planned to conduct a recruitment drive to increase reviewer numbers.

3.2.5 CRE and MPE review timelines

Lead CREs and Lead MPEs are individually given 14 calendar days in which to complete their review. A fully completed review may not be received within this

timeframe where reviewers are not assigned on the same day. Where additional CREs and MPEs are needed (depending on study and lead reviewer specialisms), they are required to complete their part in the reviews within the lead reviewer's 14-day timeline; no separate timeline is provided. Data for the total review time is taken from the time the first reviewer (CRE or MPE) accepted the review to when the sponsor was sent the completed review, and the amount of time it took sponsors to respond to queries.

The CRE/MPE timeline is an internal metric only and is not shared externally with applicants; it is used to enable reviewers to prioritise the completion of the Radiation Assurance review within their own workloads.

	Mean timeline	Median timeline
CRE Review Time	**15**	**13**
MPE Review Time	**14**	**14**
Total Expert Review Time (CRE + MPE)	22	19
Time spent with applicant	3	0

Table 5: Average CRE and MPE review times achieved during phase two, excluding the time it took applicants to respond to queries. The length of time it has taken applicants to respond to queries on average is also included. The figures in bold are for ease of comparison against the internal timeline of 14 days.

Reasons for some reviews taking much longer than 14 calendar days includes:

- A delay in assigning all reviewers for example due to multiple CREs or MPEs being required, or annual leave of available reviewers;
- Agreeing extended review timelines with reviewers due to low numbers of experts with the required specialism e.g. radiotherapy, cardiology;
- A delay in the initial queries being raised by reviewers;
- Multiple sets of queries being raised by reviewers.

The TA team will continue to monitor these timelines to ensure that this does not negatively impact on the total review timeline of 40 days, particularly given the complexity of studies and the need for multiple reviewers, that arose in phase two, which had not previously been seen in phase one. It will also be beneficial to monitor the types of queries raised by reviewers, as this impacts the date by which the review needs to be completed. Where trends in queries are identified it may be necessary for the HRA to provide further guidance to applicants and the wider research community.

3.2.6 Amendments

Radiation Assurance received its first amendment through the process in March 2019 (an amendment is classified as any change that occurs to the information as presented in Part B Section 3 of IRAS). A total of 7 amendments were submitted during the evaluation period, with 6 of these having their reviews completed and Radiation Assurance issued.

	Mean timeline	Median timeline
TAO Consistency Review Time	10	7
TAO Consistency Review Time minus queries to sponsor	**6**	**5**
Full expert review time	22	15
Full expert review time minus queries to sponsor	21	15
Total review time (Consistency Review plus Expert Review)	34	32
Total review time minus queries to sponsor	**28**	**23**

Table 6: Total amendment timelines achieved during phase two. The figures in bold are for ease of comparison against the overall timeline of 40 calendar days.

The data in the various sections in this table includes all the amendments for phase two in which each aspect of the Radiation Assurance process was completed.

Consistency review time is how long it took to complete the consistency review from when we received a complete document set. We currently aim to complete the consistency review within 7 calendar days, excluding any time it takes the sponsor to respond to any queries.

Full expert review time shows the total review time from the time the first reviewer (CRE or MPE) accepted the review to when the sponsor was sent the completed review. We currently request that the expert reviews are completed within 10 calendar days of us asking them to complete the review, excluding any time it takes the sponsor to respond to any queries, though it should be noted that the timeline shown in this section is likely to be longer than 10 calendar days because MPEs and CREs are often not assigned on the same day.

Total review time shows the time from the date of a full document pack being submitted to when the sponsor was sent the updated review.

Due to the nature and complexity of amendment to research exposures, it was agreed by the Four-Nations Radiation Assurance Working Party that it would not be possible to undertake a review of an amendment in any less time to take to conduct a full review. Therefore, we are currently advising applicants that the total review time from submission to confirmation of Radiation Assurance (amendments) should take on longer than 40 calendar days, excluding any time it takes the sponsor to respond to any queries. We will continue to monitor these timelines and where data consistently indicates that amendment reviews can be completed in less time, we will review the timelines with the Four-Nations Working Party.

4.0 Updates to the process following Phase one feedback

4.1 CRE expert involvement

As part of the ongoing development and commitment to Radiation Assurance it was identified at the commencement of Radiation Assurance that it was necessary for

there to be CRE expert involvement in the Four Nations Radiation Assurance Working Party; however, during phase one, it had not been possible to recruit to this position and it was therefore identified as a risk for the project.

The HRA continued to approach individuals from both the previous guardians' group and the wider research community in order to identify a CRE to become an active member of the Four Nations Radiation Assurance Working Party. Shortly after evaluating phase one, the HRA were able to confirm CRE membership on the Four Nations Radiation Assurance Working Party, where their advice has been sought on matters pertaining to risk, quality control and the continued appropriateness of the information and guidance provided to CREs as part of the Radiation Assurance process.

4.2 Training

Feedback received during phase one of Radiation Assurance, indicated that although mostly positive feedback was received regarding the training module. Those reviewers that had undertaken the training felt that focussing the test (at the end of the training) more on the work to be undertaken by the reviewer as part of the Radiation Assurance process and incorporating further scenarios which would assess the correct use of the generic risk statements would be more beneficial to future reviewers.

The TA team reviewed the online training and made adjustments where necessary (e.g. clarifying the process for multiple reviewers). With regards to the test, it was necessary to utilise the expertise of the Four-Nations Radiation Assurance Working Party to generate further questions relating to the use of generic risk statements.

Due to the complexity around generating further test questions, securing additional funding to amend the training and develop the additional questions, as well as providing the training developers enough time to adequately develop the new question set and for the HRA to check and test the amendments to the original training, it was not possible for these changes to be made ahead of rollout to phase two. However, no further feedback has been received from reviewers relating to the training or test, and these amendments will be in place prior to roll out of Phase three.

4.3 MPE and CRE review procedures

As recommended by the Four Nations Radiation Assurance Working Party, the MPE and CRE Review Procedures were published as part of the IRAS question specific guidance (QSG) to provide further clarity to the reviews in Part B Section 3 of the IRAS form. These replaced the current QSG about how the review should be completed, and the remainder of the QSG in this section was reviewed and updated accordingly.

5.0 Feedback received (and recommendations ahead of further roll out)

Feedback was requested from the following groups;

- Funders
- Sponsors/applicants
- Reviewers
- REC Members
- HRA Approval staff
- Sites

Those wishing to provide feedback on the process can do so by contacting the HRA via the TA team and providing feedback directly or through completing the Radiation Assurance online questionnaires.

Areas for feedback are:

- Training
- Payment
- Process
- Generic Risk Statements

The feedback received from those using the process has been extremely positive. There have been areas identified that require thought and discussion ahead of further roll out; these mainly relate to further clarification for applicants.

All feedback is summarised below.

5.1 Case Studies

As part of the feedback process, the HRA directly approached applicants and reviewers to better understand how the review process was perceived by those using it.

Case studies were undertaken by the Communications Team on behalf of the HRA. Responses received demonstrate the improvements that Radiation Assurance has made to the process of seeking MPE and CRE review.
This is evident in the number of repeat submissions from the same sponsors (both commercial and NHS).

Quotes from those approached state that;

“The experience has been professional, consistent, timely and to a good standard.”

“The reviews have been well accepted by all UK sites participating in our studies.”

“Streamlining the process though a central contact and inbox, has also taken a lot of the burden away from the research teams. Reviewers are quickly identified, and we are always kept up date on progress. Overall it has been a very positive experience for our centre.”

“We have a portfolio of early phase oncology trials and most of our trials use imaging e.g. CT or PET scans to assess how well a treatment is working. This means that all our studies will have to have Radiation Assurance before we can seek ethical review and ultimately HRA approval. We’re keen to continue using the Radiation Assurance - it’s a fantastic service.”

Feedback sought from reviewers was similarly as positive with those approached stating that Radiation Assurance was a greatly improved version of the existing process. They felt it was easier to undertake the review due to the level of information being presented to them and that a consistency review had already been conducted meaning they did not have to undertake additional checks as well as complete the review.

5.2 Participant Information Sheets

As per the review process, reviewers are required to review the information presented in the Participant Information Sheet (PIS) and where necessary make adjustments so that the information presented is suitable and clearly explains the risks to participants. Where no PIS statement has been provided, the reviewers will use the appropriate generic risk statement and provide this wording to the sponsor via the REF.

The TAOs have identified instances where changes have been made directly to the PIS and not on the REF as detailed in the MPE and CRE review procedures.

Feedback received from our reviewers has indicated that there are concerns regarding the transposing of information from the REF into the PIS and who reviews this documentation. It is the lead MPE’s and lead CRE’s role to authorise the IRAS form, where the information from the REF has been copied across, but at no point do they re-review the PIS to ensure that the required changes have been made. Concerns have been raised that if the requested changes are not included in the PIS, then this document may not be IRMER compliant.

It is proposed that from phase three of roll-out the Radiation Assurance TA team work instructions are amended so that all requested changes are made during the MPE and CRE review process, not after Radiation Assurance has been issued. Furthermore, the research exposure form and MPE and CRE Review Procedures should be updated so that reviewers do not need to include wording about the PIS in the IRAS review.

5.3 Completion of F1

F1 of the REF is completed by the applicant and includes detail on the type and number of procedures required for a study.

During phase two it has become apparent through the consistency review that where the study has been submitted by someone other than the sponsor (e.g. a CRO) or where the sponsor was external to the UK, there was often a lack of knowledge of what was required and what was considered standard of care.

This has caused a lot of additional work to be undertaken at consistency review stage by both the applicant and TAO responsible for processing the study, in order to determine what is standard of care and in getting the form completed correctly prior to assigning reviewers.

Discussion with applicants has identified that where they had previously managed studies outside of the Radiation Assurance process, they would ordinarily approach the lead centres MPE/CRE for support in identifying standard of care and the research exposure requirements, however it is not possible to do this through when submitting to Radiation Assurance.

It is planned to discuss with the Four-Nations Radiation Assurance Working Party whether there is a possibility to assign reviewers to a study much earlier in the process (either before or at consistency review stage) to support applicants in identifying research exposures and what cost implication this would have for sponsors, or if the additional workload and time impact on our reviewers would be too great.

5.4 Generic risk statements and further guidance

The generic risk statements have been well received amongst the wider research community, with sponsors opting to use the statements even if they do not submit to Radiation Assurance (feedback received from REC).

Requests have been received from sponsors and applicants suggesting that the HRA goes even further with general information for participants about the different types of exposures. E.g. “in this study you will have a CT scan, which involves these things happening to you. We will give you a dye in an injection; this could cause an allergic reaction but is unlikely” etc. This would mean that sponsors would know that they would be providing participants with appropriate information which could be copied across depending on the procedures within a study, thus further helping with set-up times and making REC review easier.

6.0 Challenges faced during phase two

6.1 CRE recruitment

It continues to be difficult to identify and recruit CRE reviewers. A total of 32 CREs had applied to be reviewers from roll out, with only 4 registering in phase two. This is the below the number initially agreed to support the process. A national shortage of CREs, coupled with the recruitment requirement for them to have experience of conducting five CRE reviews per annum, has led to difficulties recruiting in this area.

In order to address these difficulties, the HRA has agreed with the Royal College of Radiologists (RCR) that HRA registered CREs, who are members of RCR, will be able to claim one continuing professional development (CPD) point for each review they complete through the Radiation Assurance process. As clinicians are required to demonstrate that they are keeping up to date and practicing to the appropriate standards in their specialty, by documenting activities and reflecting on

learning/impacts, this agreement was an easy way to support CREs in demonstrating relevant activities for their CPD whilst acting as an enticement for those not currently registered with the HRA.

Feedback received relating to the five CRE reviews per annum requirement has indicated that this is a considerable ask for those who only review very specific trials but who are still very experienced and knowledgeable. Rather than dissuade individuals, it was agreed with the Four-Nations Radiation Assurance Working Party that CREs who contacted the HRA but had not conducted the requisite number of annual reviews would be considered on a case by case basis.

With the recruitment of a CRE Expert Advisor, the HRA has been able to identify further areas to target recruitment and additional strategies to source from our current reviewer pool.

A 5 month rolling advert has been placed on doctors.net.uk, which is a dedicated jobs website (similar to NHS jobs) for doctors and CREs. This has generated some interest, but it is not possible to tell whether any recruitment has arisen from this advert.

Following conversation with the CRE Expert Advisor it was recognised that radiology CREs can review under the umbrella of 'general radiology'. Examples of this would include reviews of plain film radiography (especially chest x-rays) and head CT scans (e.g. for trauma and stroke).
Ahead of opening to recruitment for phase three, the reviewer registration form has been updated to include a statement questioning whether applicants would be prepared to review general radiology studies and if yes, which areas they could review. Current reviewers will also be contacted and where indicated that they are happy to undertake general reviews, their details will be updated accordingly on the taxi rank.

The HRA are also discussing the value of a 'CRE hub' and whether any such community exists currently. Thus far no evidence has arisen to the contrary, if this remains true the TA team plan to create an area on JiscMail for CREs to share ideas, information and knowledge. It is hoped that by facilitating the set-up of such a forum with our current reviewer group and previous guardians, it will help identify further CREs and may generate another avenue to recruitment.

The HRA will continue to advertise and seek CRE reviewers for the process and going forward has taken the decision to review the timeline for previous reviews undertaken, if it is clearly demonstrated that individuals have the required experience and knowledge.

6.2 Site queries – identifying exposures

The question of standard of care and when an exposure becomes a research exposure is a complex issue, which often leads to differing opinions from site to site.

As Radiation Assurance has rolled out and become more used and publicised, the TA team have been managing multiple queries from individuals and teams within the

research community, but who are querying the exposures within a trial (these tend to be sites at set up stage, or sponsors who are responding to site queries). These studies have not been through Radiation Assurance and tend to have already received HRA Approval and have classified all exposures as standard of care, therefore not needing to complete Part B Section 3 of IRAS or gain lead MPE and lead CRE sign off.

The sites raising the issue feel that the exposures are not standard of care and are requesting a review of the study to determine whether Part B Section 3 should have been completed and whether without this, the study is IRMER compliant.

This involves the TA team reviewing the protocol and associated study documentation to ascertain whether;

- The exposures are undertaken at formal time points within the trial protocol schedule to assess disease status, efficacy or response to treatment;
- The information obtained from the exposure is used as data for the purposes of the study – e.g. to provide (qualitative or quantitative) data regarding disease status; and
- The exposures occur following informed consent.

The query is then passed to the Four-Nations Radiation Assurance Working Party for confirmation of assessment/further advice and guidance, prior to responding to the site and/or sponsor. This is a time-consuming process for all parties involved.

Where it is found that exposures have not been correctly identified, it is recommended to the sponsor that a substantial amendment be submitted to clarify these research exposures. As the studies do not come through the Radiation Assurance process and HRA Approval is already in place, the TA team cannot mandate this.

However, IRMER states (11d);

“in the case of an exposure taking place in the course of a research programme under regulation 3(c), that programme has been approved by an ethics committee and, in the case of the administration of radioactive substances, approved by an expert committee who can advise on the administration of radioactive substances to humans;”

As the HRA Approval process consists of a REC review and the committee undertake an assessment of the protocol which will include the ‘exposures’ then these studies would be compliant as would any sites taking part (provided that the practitioner and employer licenses under IR(ME)R allow the administrations within the protocol).

Radiation Assurance is set up to provide sponsors with greater access to MPEs and CREs to undertake reviews, ask advice of and to streamline existing processes. Unfortunately, not all sponsors choose to access the service and the aforementioned issue may continue to arise until Radiation Assurance is fully embedded as a pre-submission of HRA Approval.

The TA team has been working with experts and the Four-Nations Radiation Assurance Working Party to produce guidance to help sponsors and applicants identify research exposures in their studies. This advice is published on the IRAS website and has been publicised widely.

The TA team has also produced internal guidance to support assessment staff in identifying missed exposures at validation stage of the HRA Approval process. Targeted training will also be provided to the new HRA Approval Operations team structure prior to roll out of Phase three of Radiation Assurance.

We will continue to work with sponsors and sites to resolve issues that arise at site set up and provide guidance in order to make it easier for sponsors to know what is required of them in order to gain the necessary approvals.

6.3 Generic risk statement amendments requested by RECs

The generic risk statements document has been produced by the Health Research Authority (HRA) and the Guardians Group during the pilot to provide generic ionising radiation risk statements to be included in the IRAS application form and PIS. The generic risk statements have been designed to meet the requirements of most studies and to ensure that information is provided to research ethics committees (RECs) and trial participants in a consistent manner.

The document had undergone review from NREAP, REC Chairs and a Patient and Public Involvement Group, as well as a period of consultation in use prior to be being released as a final document.

Guidance and training was provided to HRA/HCRW staff, the devolved administrations and REC regarding the use of these statements, which all studies going through Radiation Assurance must use as per the process.

As the formal consultation period was completed prior to roll out of phase two, RECs were advised to not amend the information in the PIS where a generic risk statement had been used, unless there were exceptional circumstances for doing so, as Radiation Assurance exists to provide assurance to RECs, sponsors and sites that the information provided is accurate and appropriate.
Whilst Radiation Assurance continues to roll out, the TA team request feedback from the HRA staff managing the RECs and follow some of the more complex studies through the initial assessment process in case further queries arise. By doing this, it has been discovered that RECs are requesting changes to generic risk statements in the PIS as part of the provisional opinion, in particular to the way risk of exposure to ionising radiation is expressed in the PIS.

Where this has been identified the TA team has contacted the individual with responsibility for managing the REC to request that this is removed from the provisional opinion, as this change is against the guidance which is provided to the applicants and that the applicants should be advised that they are not required to make this change. The TA team also provide clarification of the rationale for this to be provided to the REC with a link to the risk statements for its information.

This has caused confusion with applicants and does not display a joined-up approach between REC and HRA staff.

The existing guidance for REC members has been reissued and the training for HRA staff updated following the change to the REC and assessment structure.

Feedback from REC members is encouraged so the content of the generic risk statements can be properly assessed and where necessary amended following appropriate review.

6.4 XX study

On 9th May 2019, a letter was received from an NIHR senior investigator with regards to a study that had been through the HRA-managed route of Radiation Assurance.

The non-commercial study (submitted in February 2019 by University of Southampton on behalf of the Netherland's based sponsor) was in oncology and involved nuclear medicine, radiology and radiotherapy procedures. Some of these procedures were also complex in themselves e.g. SABR, TACE, RFA.

As per the TA work instructions, the sponsor was sent the standard 'confirmation of receipt' email, confirming that the study would be HRA managed and that it may be necessary to involve more than 1 reviewer. A link to the Payments Guidance was provided, along with a statement "If you do not have the budget to cover all the reviews required for the study please contact us as soon as possible."

The study was sent to the England expert advisor for advice before proceeding, as the scans were not considered routine standard of care. The Sponsor believed the procedures to be standard of care and therefore no further detail was needed on the REF. The expert advisor advised that even if the procedures were considered standard of care, they were still classified as research exposures and should therefore be clarified to the REC, participants and for local review.

Upon completion of the consistency review, the TAO assigned to the study attempted to source appropriate reviewers. As per the work instructions, the TAO tried to source those reviewers that could cover more than one modality/specialism (e.g. one MPE to cover both nuclear medicine and radiology), however due to the availability of reviewers, this was not possible, and the review was undertaken by 5 separate individuals (3 x MPEs and 2 x CREs).

Due to the nature of the study and the complexity of the scans, the CRE and MPE reviews took some time to complete, with a lot of discussion between the reviewers over email to ensure their reviews were accurate. Generic risk statements were used for the MPE review.

Before the reviews had been completed, an email was received from the sponsor asking for clarification on the total cost for review fees, which was provided. Shortly after the TAO responsible for the study received a letter from the senior NIHR

investigator refuting some of the content of the study and refusing to pay the required fees.

Whilst further reviewing the matter, the lead reviewers for the study were contacted directly and asked to justify their advice/the information in the review and PIS. The reviewers were asked not to respond by the TA team until a QA check had been conducted by the Four-Nations Radiation Assurance Working Group.

The response received from the Four-Nations agreed with the assessment and information contained within both the review/PIS and concluded that the reviewers had completed their reviews in accordance with the relevant procedures.

This information was passed onto the sponsor and NIHR senior investigator, who still had concerns regarding the PIS information.

Subsequent email ensued, which identified further information pertinent to the trail, that had not previously been provided, namely the survival prognosis of the participant, which would impact on the information provided in the PIS.

A meeting to discuss this new information was arranged and a way forward agreed upon by all parties concerned. The PIS was updated in light of the new documented information and IRAS authorisations requested following sight of the amended documentation.

The issue took 47 calendar days to resolve and involved numerous parties, however there were learning opportunities on both sides.

- University Hospital Southampton NHS Foundation Trust (UHSFT) has 5 MPEs registered to undertake reviews. If the TAO had been informed that these reviewers were to be used, 'external' review would have only been sought from the 2 CREs necessary, reducing the cost significantly.
- Contact has been made with the Radiation Research Coordinator at UHSFT, with regards to registering radiologists through the process, this would in turn increase the number of reviewers accessible at the Trust. With both CREs and MPE available it would allow any commercial or external sponsors who work with UHFST or the CTU to request the review be undertaken by these reviewers. If it were a UHSFT sponsored study, the reviews could then be conducted via the Self-managed route.
- Upon further investigation of the email trail, the total number of reviewers needed was not mentioned to the sponsor until the final email confirming the competed review and the details of those individuals for payment. This has since been rectified and there is now a standard email to inform sponsors prior to commencing review, that their study involves multiple reviewers, so they are informed of the total reviewer fees before any further work is undertaken.
- It has been recommended by the Lead CRE for this study that a question is added to the REF alongside the median survival question as to whether the life expectancy of the entire cohort is less than about 5 years (to mirror the generic statement group) as this influences which pathway the reviewer takes

when choosing a risk statement. This will be discussed with the Four-Nations Radiation Assurance Working Party.

- The Four-Nations Working Party will also consider whether it is appropriate to put the words “up to” with the percentage cancer risk in the generic risk statements especially in those cohorts where there is a large variation in life expectancy.

6.5 Commercial sponsors – payment for reviews

Although submissions through the Radiation Assurance process has increased steadily through phase two roll out, the submission rate is only currently 24%.

Through attendance at external meetings (e.g. CCOG) and by talking to individual commercial sponsors, it has been identified that one of the stumbling blocks for commercial sponsors in submitting to Radiation Assurance is the process of payment.

The main issues appear to be that commercial sponsors are tied by the length of time it takes to implement a contract with a new trust for services undertaken, and that to set this process up is too lengthy and time consuming when they are able to (at present) gain lead MPE and lead CRE sign off outside of the Radiation Assurance process.

Prior to roll out of phase one, discussions were had with experts and the research community regarding ways to resolve the issue of payment and to acknowledge where MPE/CRE authorisation relationships pre-existed by means of a service level agreement (SLA) or vendor assessment. The HRA-managed route provides applicants with the opportunity to indicate where these pre-existing arrangements occur so that reviewers may be sought from these institutions, thereby negating the need for further contract discussions. Where this occurs, the commercial sponsors ensure the site is one participating in the study so that they may use the mNCA to include payment of review fees.

Where commercial applicants have indicated they wish to use a trust that does not have reviewers registered with us, we proactively contact the trust to discuss the possibility of registration.

Feedback received from sponsors indicates either a standard SLA (similar to the premise and set-up of the mNCA) would be beneficial or that a centralised payment system is implemented so that all sponsors have one contract with one party who then manages the payments process.

7.0 Recommendations ahead of further roll out

The roll-out of Radiation Assurance phase two has progressed well with study submissions increasing, target timelines being achieved overall, and minimal guidance changes required.

It is recommended that prior to further rollout of Radiation Assurance (phase three – all studies) commences, a minimum of 40 CRE reviewers are registered to undertake reviews (the current number registered is 32), however this is also dependant on whether these additional reviewers are able to undertake reviews of the added study types in phase three (e.g. gastro, vascular, respiratory etc) and if the existing reviewers are able to undertake general radiology reviews as detailed in section 6.2.

The current plan is for recruitment of additional CRE reviewers with the requisite expertise to begin from September 2019. During the period of recruitment, the TA team will review applications weekly to ascertain numbers submitted and be able to plan for any additional recruitment measures needed. Discussions will be had with the Technical Assurance Project Team and Four-Nations Radiation Assurance Working Party to assess progress and identify whether launch of phase three can commence.

The following should also be considered prior to further roll-out.

7.1 Identifying research exposures

As documented in section 6.2, queries arising from sites with regards to perceived 'missed' exposures is increasing. Whilst guidance has been produced to help sponsors and applicants identify research exposures in their studies, and internal guidance generated to support HRA staff in identifying missed exposures at validation stage of the HRA Approval process, these instances continue to occur.

It is planned that the TA team will provide targeted training to the new HRA Approvals Operations teams as soon as possible and no later than the roll out of phase three of Radiation Assurance. In the interim, the aforementioned internal staff guidance will be sent to all Approvals Operation staff with details regarding common misses and where to look in key documents (e.g. IRAS and protocol).

It will be necessary to continue to work with sponsors and sites to resolve issues that arise at site set up and provide guidance in order to make it easier for sponsors to know what is required of them in order to gain the necessary approvals. A series of webinars will be planned to support the guidance and to enable dialogue between sites, sponsors and the HRA. This will be ongoing and should involve members of the Four-Nations Radiation Assurance Working Party.

7.2 Participant Information Sheets

7.2.1 Amendments to the PIS at review stage

HRA registered reviewers have relayed to the TA team concerns regarding the transposing of information, following radiation review, from the REF into the PIS and who reviews this documentation. It is the lead MPE's and lead CRE's role to authorise the IRAS form, which contains the information from the REF, however they are not re-sent any amended PIS (section 5.2)

During the recruitment phase of this period of roll out, the Radiation Assurance TA team work instructions, research exposure form and MPE and CRE Review

Procedures will be amended so that all requested changes are made during the MPE and CRE review process, and to inform reviewers that do not need to include wording about the PIS in the IRAS review.

This change in process will need to be communicated to applicants and sponsors and will be made available on the Radiation Assurance pages of the HRA website and IRAS help, so this change can be embedded at the launch of phase three.

7.2.2 Generic statements for inclusion in the PIS

It has been suggested by sponsors and applicants that to accompany the generic risk statements, the HRA provides further general information for participants regarding different types of exposures, that can be used in the PIS.

It is proposed that this would work in a similar way to the generic risk statements, where the sponsor or lead MPE/CRE selects a bespoke statement relating to the procedures in a study (section 5.4).

This recommendation will be discussed with the Four-Nations Radiation Assurance Working Party and HRA guidance team to determine whether this would be a proposal that the HRA could support or whether a document like this would be too prescriptive and variable.

7.3 Assigning of reviewers prior to consistency review

Additional work is occurring for both TAOs and applicants at consistency review stage, as through the Radiation Assurance process applicants do not have early access to MPEs/CREs to support in the identification of standard of care procedures and when these become research exposures.

It is an agenda item for the August Four-Nations Radiation Assurance Working Party meeting to discuss this issue and the implications for and against implementing an early support mechanism for sponsors/applicants If this cannot be accommodated, due to cost, time impact, workload issues, an alternative solution will need to be sought/discussed so this issue does not escalate and have a negative impact once Radiation Assurance is fully embedded.

7.4 Payment

The issue of implementing contracts is not one that can be easily solved. It is important that discussion is generated regarding next steps and how best to support our commercial sponsors. Conversations will need to occur to determine the crux of the issue and what solutions there are.

Following initial review (consultation with a small percentage of commercial sponsors) it is apparent that the preference is for centralised system, failing that an SLA or contract similar to the mNCA.

A centralised system would be advantageous as both applicants and reviewing trusts would deal with only one central party, rather than numerous contacts for different

study reviews. However, this would require investment (monetary, time and staffing) and may have implications with regards to liability of payments (e.g. late payment or where there is a dispute

A standard SLA may be easier to generate but would require legal review by numerous parties, which could take years to reach an agreement and may not wholly solve the issue.

The TA team will continue to work with commercial sponsors to identify trusts they already have working relationships with. Where those organisations have reviewers registered, they will be approached to undertake study reviews. Where no reviewers are registered at the suggested organisation, the HRA will approach the R&D office to promote application to the process and the benefits for the site from being involved with the Radiation Assurance process.

It is recommended that the issue of payment is explored further, and discussion generated both internally and externally to identify areas of work regarding the wider contracts and payments issue in the NHS, where Radiation Assurance can dovetail or learn lessons from.

7.5 Study submissions – working with sponsors

It is anticipated that launching phase three of Radiation Assurance to accepting all studies taking place within the NHS/HSC will increase study submissions, however, it is still crucial that the HRA promote the process and the ability to feedback whilst in testing phase.

The TA team will work with Approvals Operation and Approvals Programme staff to promote Radiation Assurance and encourage submission and feedback throughout the research community.

The TA team intend to target key sponsors (both commercial and NHS) to invite them to work alongside the team in continuing to test the process ahead of formal implementation into HRA/HCRW Approval.

7.6 Timelines

Although Radiation Assurance is currently achieving its timelines, there is a perception in the wider research community that the process is lengthy and can be completed quicker outside of it. It is recommended therefore, that the information available to sponsors regarding timelines is publicised on the Radiation Assurance webpages and should include a breakdown of what the review timeline entails i.e. validation, seeking reviewers of appropriate specialisms and completing the expert review.

The TA team will continue to monitor all timelines associated with the Radiation Assurance review, to identify where delays occur and implement solutions where possible (e.g. further detailed guidance, training). To support reviewers in completing their reviews in a timely fashion the TA team will continue to update them

regarding any change in the deadline, particularly where queries are raised with the applicant.

7.3 Staffing levels

The TA team is a relatively small team undertaking an extremely large role (1 manager, 1 senior TAO, and 4 TAOs, with one currently on secondment).

The responsibility of the team is to progress both Pharmacy and Radiation Assurance and embed them into the HRA Approval process. Once fully implemented they will continue to manage study submissions and oversight of both processes.

Whilst staffing levels have been sufficient in the purely developing stage of rollout, the launch of both Pharmacy and Radiation Assurance, alongside the continuing developing of the processes has meant that at times (sickness, annual leave), the team has felt extremely stretched and the study submissions are currently only a small fraction of what should be received through the process.

As both Assurances progress to full roll out and implementation, it will be necessary to look at staffing levels to ensure provision of the same level of quality that is currently seen and expected of studies progressing through Radiation Assurance.