Health Research Authority

Evaluation of the ‘Single Pharmacy Technical Review’ pilot undertaken in collaboration with Cancer Research UK and the UK Experimental Cancer Medicine Centres

Contents

1.0 Executive summary

The Health Research Authority (HRA) and Cancer Research UK (CRUK) have collaborated to initiate a process of single technical pharmacy reviews within the UK Experimental Cancer Medicine Centres (ECMCs). CRUK have undertaken a programme of activities to streamline the set-up and delivery of studies through the ECMCs. One component of that programme was to focus on pharmacy and radiation aspects of the studies run through these centres. As part of its remit to streamline and coordinate the research process, HRA welcomed the opportunity to test a process that could in due course be rolled out more widely. CRUK and HRA therefore jointly designed a process for single technical reviews. When the Department of Health approved the HRA's business case for implementing HRA Approval as a new simplified process for study set-up, it was recognised that the pharmacy and radiation technical reviews would in due course be incorporated into the HRA Approval process.

The collaborative project on pharmacy technical reviews with CRUK (termed the Single Technical Pharmacy Review project by CRUK) was therefore established as a formal pilot undertaken from August 2014 to April 2015. This report evaluates the outcome of that pilot.

During this period 38 reviews were completed. These 38 studies listed a combined total of 207 sites within the ECMC network. Up to now these sites would have had to individually carry out full pharmacy reviews for these studies.

The experience with the ECMCs combined with that in regional initiatives has demonstrated the feasibility of using NHS professionals based across a number of institutions to complete single reviews. It has demonstrated that the provision of all relevant information by the sponsor representatives, which has previously frequently not been included or has been unclear in the protocol, is key to the utility of the review, and the timescale within which it can be undertaken.

The next step in England is to confirm operational arrangements for a controlled expansion of the process beyond the ECMC studies, aligned with implementation of HRA Approval Cohort 4. Further discussion with the devolved administrations will consider the potential for a UK-wide system of single technical reviews.

The HRA is very grateful to all the professionals and participating organisations that have completed reviews and supported the development of the project, and to the sponsors who put their studies through the pilot process.

2.0 Background

Pharmacy review of new studies has been identified as a possible hurdle in site set-up of Clinical Trials of Investigational Medicinal Product (CTIMPs), and an area where there is a lot of duplication in the work done by the sites. Implementing a system of single reviews of new studies could achieve the following benefits:

- Releasing staff time currently spent on completing parallel reviews and resolving queries at multiple sites.
- Endowing a reviewer with authority to give useful feedback and, if necessary, to challenge the study team at an early point of site set-up process.
- Give greater clarity to study teams at the outset of the information requirements for sites to review and set up studies.
- Reduce the number of queries which sponsors receive from pharmacy departments.
- Streamline the local pharmacy capacity and capability assessments.

There have previously been several projects in the UK for pharmacists at different Trusts conducting joint reviews on studies. Notably the University College London (UCL) Partners Harmonisation Project has included a single review process since 2012, which has processed more than 500 studies. Scotland had been developing a single process across the Health Boards which was aligned with this project. As part of the HRA Approval programme it is planned to implement a system of single technical pharmacy reviews across all studies in the NHS in England.

The project also acknowledges valuable input from the "Guidance on information requirements for local pharmacy review of research studies" completed by National Institute of Health Research Clinical Research Network (NIHR CRN).

3.0 Overview of the review process

The ECMC single pharmacy technical review process involves sending out new Phase I or II cancer CTIMPs for review by a trials pharmacist working within an ECMC-partner NHS trust. These reviews are then shared with the participating sites and they will proceed with completing their local reviews. This removes duplication in obtaining the key information from the study documents and corresponding with the sponsor to get clarifications and missing information.

During the period from August 2014 to April 2015, 51 studies were sent out for a single review, of which 38 were completed by the end of this period. The completed reviews corresponded to 207 total ECMC sites which will be setting up the studies. During this period there were a small number of studies which were initially sent to a reviewer, but it was decided either by the sponsor or the HRA to withdraw the application from the single review process. These are not counted among the 51 reviews. This was either due to identifying specific features of the IMP that required particular assessment, or for studies with a small number of sites, where it was identified that it was no longer of much utility for the remaining sites. The remaining 13 studies completed their review process after the cut-off date for analysis for this report.

4.0 Project development and implementation

4.1 Collaboration between HRA and CRUK through the ECMC network

In response to feedback from sponsors and pharmacists, and building on developments already underway in parts of the UK, the HRA put forward a proposal to streamline pharmacy review of research studies. The ECMC network, which is jointly funded by CRUK and the UK administrations, looks to foster collaboration between the clinical professionals across their network. The two organisations agreed to collaborate on the implementation of a single review process across the UK ECMC network.

4.2 Initial development, consultation and workshops

In proposing the new process, the experience of UCL Partners, Scottish Health Boards and a CRUK project were drawn upon. Workshops were organised in spring and summer 2014 for the pharmacy departments who would be participating in the process; a set of documents were circulated for comment and feedback. These workshops led to changes to the process and document set which was then released to all participants in August 2014, with the project opening to new studies for review.

A set of eligibility criteria was agreed for studies giving a manageable subset of all cancer trials. Additionally it was agreed that reviews would not be initiated after the REC submission, but by a request from the sponsor representative. It was agreed that reviews could take place before REC and MHRA submissions had been made.

It was decided after the summer workshop that there would be a group of pharmacy professionals who would support and contribute to the ongoing development of the process. Five “Pharmacy Guardians”, four from England and one from Scotland, have been instrumental as a point of contact for the HRA and for providing professional input. The Pharmacy Guardian Group was constituted of the five Pharmacy Guardians plus representatives from the HRA and CRUK.

4.3 Further development during implementation of the project

Following a period of around six weeks the progress of the project was reviewed with the Pharmacy Guardian Group. The number of reviews requested had been lower than the number of eligible studies known to be coming in from REC submissions. There had not been any review requests that could be processed before regulatory submissions. It was therefore agreed that sponsor representatives would now be approached following the REC submissions and that the expected time of review would be after regulatory submissions. It was also agreed with the UCL Partners team that they would refer to the HRA any new studies that they judged may be eligible so that single reviews would not be duplicated between the two processes. Following these agreements the number of studies going through the process increased rapidly.

In autumn 2014, following discussions at a Pharmacy Guardians teleconference an information sheet was added to the document pack to accompany initial contact to the sponsor representative. In November 2014, the Pharmacy Guardians came together to consider the initial reviews. They recommended changes to the review form that were implemented in January. Also during the meeting four completed forms were reviewed and it was discussed how the review form was most usefully populated, which fed into the accompanying guidance in development.

During February and March there were events held around the country with R&D and trials pharmacy staff to discuss the proposed review process and its coming implementation for all trials. Following feedback received from these events and queries made during reviews, further changes to the review form were taken forward for consideration.

Feedback from reviewers as the process has continued has indicated that in many instances key information was missing from the documentation submitted to the HRA. A frequent issue was that the Pharmacy Manual was not provided by sponsors. In response, HRA clarified the requirement for all sponsors to submit a Pharmacy Manual wherever applicable before sending their study on for review. Where sponsors are unable to provide a pharmacy manual, it is made clear to them that the reviewer will nonetheless require specific information which would normally be expected to be within the manual.

5.0 Experience from the project

5.1 Timing of reviews

At the meeting with ECMC pharmacists on 15 July, before the evaluation period went live, different opinions were given on the most useful scope of a single pharmacy review process. The proposal taken to the meeting was that there would be a single review at a single time-point which would take place after the final document set had been prepared for submission to MHRA and REC. However it was proposed by some at the meeting that because pharmacy departments were reviewing studies as part of the site feasibility and selection process that a single review process could start at this time. It was therefore agreed that requests for reviews could be taken up prior to regulatory submissions. In the next six weeks the HRA were contacted about one study before REC submission, and in that case they were unable to get a document set from the sponsor before REC submission. It was discussed with the Pharmacy Guardians at a teleconference in September and it was agreed that the main entry point for studies would be following REC submission. Further to the communication of that decision to the reviewers, no further requests were received to review studies before regulatory submissions.

Once the process was running it was found that a significant proportion of reviews were delayed until some time after the regulatory submissions whilst waiting for a full document set to be available for review. This is discussed further below.

5.2 Documentation required for review

Through the process there has been useful experience on the documents that are made available for review. The following documents are submitted to REC and/or MHRA, so can be requested for the review:

- Protocol
- REC form
- Investigator brochure (IB)/Investigational Medicinal Product Dossier (IMPD)
- Summary of Product Characteristics (SPC/SmPC)
- Sample labels

There are two other document types that may be received from sponsors on occasions, but have not been generally required for reviews historically:

- QP documentation – some sponsors have QP documentation on drug manufacture available to send to sites at the point they will review the study. This has only been seen in a small number of trials in the process. In other cases the first receipt of QP documentation will be with the first IMP delivery.
- Safe handling and storage documentation (i.e. related to health and safety requirements) – for some drugs in an early phase of development there may be additional documentation accompanying the IB/IMPD/SPC to cover safe handling etc. instructions. This has not been observed for any of the studies in the process.

This leaves the class of documents that this document will describe as Pharmacy Manuals. There is no standard nomenclature for these documents, and this phrase is used here to cover any document not submitted to REC and MHRA that accompanies the Protocol and includes additional information on the IMP for pharmacy departments. Pharmacy Manuals will not be present for all CTIMPs. For the early stage cancer trials included in the process almost all sponsors planned to release such documents.

Feedback received from pharmacy reviewers is that it is very desirable to include the Pharmacy Manual in the review if possible. It is an opportunity to check that the document itself is clear and consistent with the remaining documents as part of the review. Another consideration is that otherwise the reviewer will have to raise queries to get the information that the sponsor intended to present through the Pharmacy Manual, delaying the process further.

It has often been practice for Pharmacy Manuals to be made available only a period of time after regulatory submissions. This applies to both commercial and non-commercial studies, although the interval can be longer for non-commercial. During the pilot when the pharmacy review has been a stand-alone process it has been possible to wait until the study team have reached the point of writing a late-draft or final Pharmacy Manual before sending the study on for review. For future inclusion of single pharmacy review in the HRA approval process this will pose challenges.

5.3 Pharmacy Guardians

As previously stated, five pharmacy professionals volunteered to help support the development of the process with the HRA and CRUK. At later points this group was supported by another pharmacist from Scotland and the manager of the harmonised reviews taking place in CRN: North Thames, who was on part-time secondment to the HRA. The Guardians held a series of teleconferences in September and October while the initial reviews were being processed and the process was being established. They then reduced the frequency of their meetings to every couple of months, with two longer face-to-face meetings to consider the course of the review process.

The Pharmacy Guardians have been essential as a reference group while establishing the system. After looking at the initial reviews they were able to recommend changes to the review form, also assisting in the development of other documents. They looked at a subset of the completed review forms so that as a group they could make recommendations on the best use of the form in order to produce guidance on its completion.

5.4 Quality Control

During the evaluation period experience was gained on the approaches that could be taken to assuring the quality of the reviews completed. Assurance can come from three routes:

- Local sites receiving forms are directed to feed back if they have any concerns about how the forms are completed.

- The staff coordinating the reviews can check that the answers to the questions address the question as given and are in a clear format.
- Review forms can be sent to a designated second reviewer or Guardian to check through the work done by the original reviewer.

In the UCL harmonisation process they did not feel that the third option was required with their group of reviewers, which was smaller and regularly brought together. During the ECMC reviews the Pharmacy Guardians all looked at the first four review forms completed before a meeting in November 2014. This was to check the quality they were being completed to and consider how reviewers could be guided to use the form. This has fed into the development of more detailed guidance on using the form.

No formal QC process has been initiated to date and this will need to be considered in further roll-out.

5.5 Allocation of reviews and specialisms

At sites with a large trial portfolio it is common practice for clinical trial pharmacists to work in particular specialisms. In particular, common specialisms are oncology (sometimes split into solid tumour and malignant haematology) and paediatrics. Many of those consulted expressed the view that there could be value in having a single reviewer who has experience of the specialism of the trial. On the other hand it is intended that the focus of the review is technical rather than clinical questions about the trial. UCL Partners has successfully proceeded with allocating reviews without regard to specialism, with some training given on the particular concerns for different specialisms. By splitting the trials by specialism it may be challenging to distribute reviews evenly. It was agreed in discussions that many trials will not require specialist knowledge, while there are some complex trials that those without direct experience of similar projects may not wish to review. As the ECMC review process was limited to oncology, and the reviewers were all from these specialisms, it gave limited further experience on this topic.

5.6 Funding and standard of care issues in review

There was debate at the workshops and then at the Pharmacy Guardian Group meetings about the expectation on the reviewers to look at issues of funding and compatibility of the study with current standard of care. The conclusion was that the process was to be kept as a technical review, and not reach the point where detailed knowledge of current treatment policies in the NHS is a pre-requisite to be a reviewer. A field was included in the review form to allow any issues that the reviewer had picked up to be flagged for participating sites. However clinical review responsibility has remained with sites, with a prompt on the local clinical feedback to consider compatibility with local practice. 17% of local queries raised which the HRA was informed about were related to excess treatment costs and funding and therefore the management of this issue may need to be revisited in future.

5.7 Commercial funding template and pharmacy reviews

In UCL Partners the reviewers completed the pharmacy section of the NIHR CRN industry costing template. At the summer workshop this was discussed. As a number of sites did not use the charging framework set out in the costing template it was agreed that this would not be a requirement for the pilot. The HRA Approval process will include a requirement for the industry costing template and so integration with the pharmacy review process will need consideration.

5.8 Single site studies

The procedure agreed for the ECMC single reviews was that if there was only a single site in the UK then the single site would complete the review. They would however complete the same review form, so that there was a single process, and so that the review form would be available if another site joined later. This was due to the potential to increase the workload on the sponsor from dealing with staff from a single institution to dealing with staff from two institutions. The proportion of single site trials that went through the process was only 8%. Single site studies were not prioritised for inclusion and largely depending on the site choosing to complete and send us the form. The estimated proportion of all clinical trials that are single site is 32%.

5.9 Sponsor pharmacists and non-commercial studies

For non-commercial studies it is common for an NHS-based clinical trials pharmacist to have a considerable contribution to the whole development of the study, including development of the study Protocol and Pharmacy Manual. It was queried at the workshops what the role of this pharmacist should be in completing or supporting the single review. For non-commercial studies that had previously had pharmacy input there were still cases where the single reviewer had questions or clarifications about the documentation sent. The Guardians discussed this in November, and they gave the opinion that the sponsor pharmacist is part of the study team and there is therefore a significant benefit in having someone from outside look over the documents and query anything they do not find clear, thus avoiding delays at other sites.

5.10 Chemotherapy and Pharmacy Advisory Service

A number of non-commercial clinical trials in cancer and malignant haematology receive support from the Chemotherapy and Pharmacy Advisory Service (CPAS), which is supported through the CRN and gives a valuable contribution on study design. In early 2014 two representatives of the CPAS committee were consulted and recommended that the CPAS reviewer complete the single review form as far as possible when completing the CPAS review, and then complete the form at a later date when full details were available. This recommendation did not take effect for any reviews that occurred during the evaluation period, as no such studies were received. If it is to be implemented in future then the direction given to CPAS reviewers will need to be considered and agreed by the CPAS Committee based on the benefit derived by early partial technical review as part of the initial CPAS review. This would also need to be checked for consistency by a

pharmacy reviewer when the full study details are known to ensure that the earlier technical review is still valid.

6.0 Evaluation of the ECMC Single Technical Pharmacy Review process against the principal aims of the project

6.1 Single review process

During the evaluation period seventeen reviewers at different NHS institutions completed the reviews. Reviews were allocated as evenly between the reviewers as possible. Reviews were sometimes allocated to sites that were not participating in the study, however, in allocating reviewers it was an objective to allocate to participating sites where possible. Reviewers were also able to respond and say that they were not able to complete a review at that time due to, for example, annual leave. Due to reviewers rejecting some reviews the number of technical reviews that each individual conducted in this period varied from 1 to 5.

The reviews only took place once the HRA coordinating staff were able to contact the sponsor and ascertain that the information required for pharmacy review had been assembled. The documentation would then be sent to the reviewer either by email or, later in the process, via an online collaboration site (until HARP can be developed to accommodate this process).

Reviewers were asked to look over the documents and either raise queries or complete the review within 7 calendar days. Where queries were raised the extent of the queries varied significantly from minor clarifications to requesting additional documentation, which was sometimes not yet finalised and ready to be submitted, in order to provide the information required to complete the review.

	Time (calendar days)		
	Range	Median	Average
All completed reviews	1-139	14	25
Length of time to queries being raised	2-61*	9	13
Completion time where no queries were raised	1-139**	16	24
Completion time where queries were raised	7-103	21	22

Notes:
The data above reflects the total time taken and does not include any clock stops
**There were difficulties assigning a reviewer for the study which took 61 days for queries to be raised. After this study, the longest time for a query to be raised was 28 calendar days.*

***For the study which took 139 days to review there was due to be a change in national funding for one of the drugs which would affect the review*

Although the initial timescale aimed for was not achieved, the timescales that were achieved should be viewed in relation to the total timescales for trial set-up. Additionally, it is important to note that the single technical review is running in parallel with the current process where other studies will still require a technical review at each site, and therefore limited time is released during the pilot phase, and this may be a contributing factor for the timelines not being achieved.

The ECMC review process has allocated reviews to individual reviewers at a rate of around 6-8 per year. It is important to note that as these studies are early stage cancer trials that they are typically more demanding than other studies due to the high proportion with unlicensed drugs, cytotoxic/cytostatic drugs, drugs given as infusions rather than orally, and other considerations that can arise from cancer trials. It was important to test the process with these trials early on, to ensure that these complexities could be addressed in the single technical review.

6.2 Local reviews and set up

Initially it was proposed that sites complete local reviews immediately following the single review in all cases. It was fed back that this could lead to pharmacy departments reviewing studies a long time before likely set-up at site, an interval of years in some cases, due to the timelines for some CTIMPs setting up a large number of sites. They would be reviewing the study before any local issues had been considered by the study team. Also some sites wished to only complete reviews after regulatory approvals were in place, when approved documents were available. It was agreed that sites should complete local reviews at a time of their choice.

The outcome of the single technical review was sent to all named participating sites, to enable completion of the local review. A total of 88 completed local reviews were reported to HRA, only 40% of the total sites expected. This may be because the local review was not required due to the timing of local site set-up. In other cases pharmacy departments have reviewed studies locally before they knew the study would be going through the ECMC single review, so the full benefit of the new process was not achieved

For these 88 confirmed local pharmacy approvals, the studies are known to have progressed to NHS permission by the end of April 2015 in 37 cases.

Multiple pharmacists have informed the HRA of the average time it takes them to review and set up a study. From this it is possible to estimate that the average time spent conducting the full local review and set-up at each site under the existing system is 7.5 hours, whereas when the pharmacist is able to rely on a technical assurance conducted elsewhere the total time needed locally to set-up a study is only 2.5 hours. This equates to an estimated saving per site of 5 hours and would mean that the estimated pharmacist time saved preventing duplicated technical reviews for all sites thus far is 750 hours.

7.0 Recommendations for further implementation and roll-out

7.1 Further roll-out – study types, locations and IT support

The Pharmacy Assurance process is currently accepting Phase I and II oncology trials where the lead site is part of the ECMC network. Feedback from pharmacists has indicated a limited effectiveness partly due to the single technical review not being conducted for all studies and it would therefore be beneficial to widen the scope of the single review process to at least include all phases of oncology trials in the ECMC network. This may also be a good time to widen the scope of trials submitted into the process to include studies where a non-ECMC site is the lead site in order to give more Trusts experience of the process and to incorporate their feedback into its development. Alternatively, to provide experience of how specialisms could be used in the taxi rank it would be constructive to involve non-oncology trials at this point and using the ECMC network would be a useful way to do this.

Whilst it is important that as many sites as possible experience the pharmacy assurance process in a further roll out, it needs to be recognised that the correct IT support also needs to be in place. In advance of developing HARP to support technical assurances, the HRA procured 25 licences for an online collaboration site so that pharmacists can all access the study documentation online, all of which are currently in use. Further licenses for the collaboration site will cost more but will allow more sites to participate in the pharmacy assurance process. Use of the online collaboration site was procured specifically to facilitate the review process and to prevent pharmacists' inboxes being filled by large documents.

i. Options (IT)

1. Procure additional licenses for the collaboration site to allow more sites to participate. This would expose more sites to the current interim IT solution, which may be confusing and ultimately impact on the final roll out.
2. Do not procure additional licenses for the collaboration site and include sites outside of those currently participating from the ECMC network; this will increase the difficulty in allowing sites access to documentation, which will probably have to be sent by email.
3. Do not procure additional licenses for the collaboration site and only include the current participating sites in the ECMC network in the next phase of roll out.

ii. Options (study types)

1. Limit the roll out to the ECMC network by including:
    a. All oncology CTIMPs or;
    b. All oncology CTIMPs and Phase I and II non-oncology CTIMPs or;
    c. All CTIMPs.

2. Roll out to sites outside of the ECMC network:
    d. Include only Phase I and II oncology CTIMPs or;
    e. Include all Phase I and II CTIMPs, oncology and non-oncology.

3. Include a mixture of the above study type options e.g. 1b and 2a.

iii. Technical Assurance Team Recommendation

It would be highly desirable at this stage to include sites outside of the ECMC in the taxi rank, however, this would require expansion of an interim IT solution, which may impact on acceptance of the long term roll out. It is proposed that the next phase of roll-out should be for all oncology CTIMPs and Phase I and II CTIMPs in non-oncological diseases in the ECMC network. This will give the maintain continuity in terms of IT system and build up the experience of the centres to other studies, as well as expanding the pool of reviewers in preparation for further roll out (see also below recommendation regarding specialities). In parallel to this, work should be started on HARP development to facilitate a further roll out to new organisations.

7.2 Numbers of Reviewers

Extrapolating from the frequency with which reviews have been allocated in the later stage of the project (equivalent to 8 reviews a year per reviewer), around 100 reviewers would be needed to review the expected maximum of 800 CTIMPs a year (see Appendix). However, it should be noted that during this pilot, the review activity has been conducted in addition to continuing to undertake full reviews of all other studies not falling within the scope of the pilot. It should be noted that if single-site studies continue to be reviewed by the site itself then only 500-550 studies a year would be allocated through the taxi-rank. As previously discussed, the ECMC studies may be more onerous to review than a more general clinical trial. An alternative example comes from UCL Partners, where 15 reviewers have succeeded in completing single reviews for 225 studies a year, which would extrapolate in a national setting to 15 reviews a year per reviewer and around 55 reviewers. In addition it is known that trials pharmacists at large Trusts are often completing full reviews of far more than 15 studies a year on behalf of their Trust. This would give a lower possible figure of around 50-60 reviewers.

Thus previous experience would give a window of 50-100 reviewers, with the upper end placing fewer burdens on individuals. The Pharmacy Guardians have suggested that in order to increase the potential pool of reviewers available that it may be possible for some Pharmacy Technicians to be reviewers where they have the correct level of expertise, experience and qualifications. It may also be taken into consideration that there may be a benefit in as many Trusts as possible having a reviewer, though feedback from pharmacists has indicated that there is concern that there may be a great burden placed on smaller Trusts which have fewer pharmacists and fewer CTIMPs. There are 170-180 Acute and Specialist Trusts, and many more Mental Health and Community Trusts, although the latter generally conduct fewer CTIMPs.

i. Technical Assurance Team Recommendations

1. Plan for a larger number of reviewers once full roll-out is in place in order to ensure that a reviewer will always be available. With smaller numbers of reviewers it will be more difficult to allocate reviews if people are on annual leave, for example.
2. Request larger Trusts (such as the ECMCs) to put forward more reviewers than smaller sites as they will have capacity to take on more reviews. If this is not possible then the larger sites should at least be asked to conduct more reviews than smaller sites.
3. Further reviewers should now be identified for the next stage of roll-out in order to ensure that reviewers can be found expeditiously and to ensure that the burden on current reviewers is not increased too much with the additional workload.

7.3 Specialisms of Reviewers

It is important to recognise pharmacists' views in order to gain their support and ongoing collaboration with the process and there may therefore be value in allocating reviews according to specialisms as suggested by the feedback currently received. However, it also needs to be considered that the Technical Assurances team will be required to manage allocation of reviews and therefore too many specialisms is likely to be detrimental to this due to a smaller pool of reviewers available per specialism; recruitment of reviewers to the individual specialities will also be more challenging.

It has been suggested by pharmacists that if specialisms are to be used this could just be split between oncology and non-oncology as pharmacists who work with non-oncology studies are often reluctant to cover oncology studies due to their lack of specialist knowledge. A further suggestion that the specialisms are in aseptic and dispensary studies has been well-received by Chief Pharmacists.

i. Options

1. Do not use specialisms. Training should be provided to those who require it in specific areas of expertise.
2. Use specialisms – split studies by oncology and non-oncology.
3. Use specialisms – split studies by dispensary and aseptic.

ii. Technical Assurance Team Recommendation

Use specialisms and split by oncology and non-oncology as this is a familiar way for pharmacists to work. It will help to increase support of the process and will allow reviewers to work swiftly within their areas of expertise without the need for additional training. If the decision is taken in the long term not to use specialisms the HRA will need to ensure that appropriate training is developed and is in place for reviewers so that they are both confident and comfortable in undertaking reviews outside the normal professional practice.

7.4 Reviewers – other considerations

As discussed above, less than half of studies were completed or had queries raised within 7 days, with the technical review taking approximately 5 hours to complete, indicating that reviewers currently do not have the capacity to complete reviews within the timescale. Feedback so far indicates that only half of pharmacists thought that 7 days was enough time, and the other half thought that this was not enough time. However, the optimum timeline in relation to completion of the HRA assessment and the REC review as part of HRA Approval is not yet clear.

Concern has been raised by some pharmacists that the reviews are currently not conducted at a time when they would usually be done, and so are perceived as "additional". This reflects that the ECMC centres are often the lead or sponsor for CTIMPs, and the pharmacists at these sites will get involved in the study on behalf of the sponsor as well as undertaking activities in their role supporting the hosting of the study at the site. Sharing the technical reviews across a wide pool of reviewers will, however, reduce the burden of what might be perceived as "additional" reviews. It is important to note that when all commercial and non-commercial CTIMPs are going through HRA Approval, it will be important that sponsors have a clear and consistent process for providing the necessary information as part of the single application to HRA. A suggestion has been received that the lead/ sponsor site in a trial is allocated the review, however the same few sites tend to be the lead sites in CTIMPs and this would therefore place a greater burden on them. It would also mean that any issues with a non-commercial study that had not been addressed in the sponsor process would not be independently identified in the single technical review, potentially causing delay and duplication at local sites.

i. Technical Assurance Team Recommendations

1. Discussions should be had with Chief Pharmacists to ensure that time is allocated to perform the technical reviews; these discussions should reference the fact there would still be fewer reviews across each organisation, and that those few sites would already be undertaking reviews.
2. The review time should be reviewed as part of the overall HRA Approval process, to determine an appropriate target timeline for technical reviews.
3. Only sites which conduct a study should be used as reviewers wherever possible;
4. For single site studies, the technical review should be allocated to that site;
5. Non-commercial studies should be reviewed by sites other than the lead/ sponsor site to incorporate an independent perspective.
6. In line with the prevailing guidance on attribution of costs for research activities, the single technical review is classified as a research cost. Accordingly, it should be costed into the study once formal decisions are made about the appropriate amount payable, and the payment framework to facilitate timely invoicing and payment. Early discussions at HRA Collaboration and Development Forum, and other meetings such as with NIHR funders have seen this outline proposal meet with no objection, not least because likely sums payable are unlikely to represent significant outlay for sponsors. More importantly, it should also be considered that payment for the technical review will raise expectations and standards in the

quality and timeliness of the review. A basic principle agreed by parties to date is that any payment made for the single review should be made to the reviewer's department, and that distribution of this payment should be made in line with current local practice. The HRA has no remit to specify how departments manage such income.

7.5 Guardians

In addition to providing professional leadership for the reviews and acting as a reference group, a group of Pharmacy "Guardians" would play a key role in supporting the training and QC processes for a single review process, and so giving cohesiveness to a review process involving a large number of reviewers. The Guardians would be able to provide an external QC review to increase assurance in the process. It has been suggested that the HRA could perform the QC processes themselves, however, as the review is in itself technical it would be difficult for the Technical Assurance Officers to be able to ensure, other than that all fields in the review form had been completed, that the review was satisfactory for use by other organisations to allow them to perform local reviews. There may be a role for the HRA to perform in the future but in the initial roll out it is important to gain as much support as possible and to ensure that the process is robust.

The experience in the ECMC process is that reviewers have not sought to contact their Guardian unprompted, and a network of practice will need to be planned and to a degree directed if it is desired. The NIHR CRN has existing email groups and the NIHR Google group to allow pharmacists to seek advice from their peers.

The number of Guardians will be driven by two considerations. In their role as a steering/reference group for the implementation and management of a process a group of 5 has been found to be effective. It can be reasonably expected a larger number will also be manageable, which may be required when further roll-out occurs to account for additional specialisms and, potentially, different types of NHS organisations. In their role in supporting and feeding back to the other reviewers the ECMC reviews have not provided much evidence on how this will operate. UCL Partners also provide little evidence as they have had a central approach to training and support with little burden on the Guardians. It has been suggested that there should be at least one Guardian for each CRN area, to match existing local networks and structures. If there were 100 reviewers then the largest CRNs may have up to 10 reviewers, which may require two Guardians. This would give 15-20 Guardians in total.

Due to the additional leadership role it has been argued that Guardians should be paid a fee for their services.

i. Technical Assurance Team Recommendations

1. Invite England-based ECMC Guardians to become Guardians on the new group.
2. Invite (subject to Chief Scientist Office's approval) ECMC Guardian from Scotland to be on Technical Assurances Board.
3. Utilise the current CRN networks to identify Guardians.

4. The number of reviewer per Guardian should be similar nationwide. Either there are multiple Guardians in CRNs where there are a lot of reviewers, or individuals act as Guardians for multiple CRNs where there are fewer reviewers in said CRNs.
5. Each region of Guardians and reviewers should have one HRA Technical Assurance Officer to act as their main point of contact for any issues to be raised. Regional meetings could be held with Guardians and reviewers to discuss and resolve any issues. Any issues which could not be resolved regionally could then be escalated to the national Guardians group who would represent their reviewers.
6. The Guardians, as well as acting as a point of contact and to provide professional leadership to reviewers in their area, would QC the technical reviews.

7.6 Documentation requirements to progress the review

As the process progresses it is important to ensure that validation criteria regarding documentation requirements are agreed and adhered to. The current document set requested, following proposals from pharmacists, is:

1. IRAS form
2. Protocol
3. IB and/or SmPCs
4. Labels submitted to the MHRA, if available
5. Pharmacy Manual, if available

The first four documents are easy to acquire. The fifth, the Pharmacy Manual, is more difficult because it is often not ready until quite some time after the REC application is made, and can even be months after the favourable opinion is issued, in the current context when REC applications are often made prior to embarking on study set-up at sites. Furthermore, not all studies will have a Pharmacy Manual or even require one. The Pharmacy Manual has been requested for all studies in the pilot. However, it should be remembered that the pilot process only involved Phase I and II oncology trials. Whether Pharmacy Manuals will be required in the majority for other study types remains to be seen.

Further work across more study types is required to understand what information from Pharmacy Manuals is felt to be needed by reviewers, so that sponsors can, if necessary, ensure that they start acquiring and preparing this information ready for submission through HRA Approval.

i. Technical Assurance Team Recommendation

Work with the Guardians now to establish what information is required to enable reviewers to complete the technical review. This can also act as validation criteria for the Pharmacy Assurance aspect of HRA Approval.

7.7 Timing of submissions in relation to HRA Approval

The HRA is currently accepting some trials for the Pharmacy Assurance prior to REC submission, though very few trials have been received and reviewed in this manner. It could be argued that trials should wait to submit for Pharmacy Assurance until the main submission through HRA Approval. However, as the Radiation Assurance process will be conducted pre-Approval submission, it could also be argued that the Pharmacy Assurance could be conducted pre-Approval submission. Feedback from sponsors has indicated that the earlier the technical review can be initiated, the better, and sites have fed back that they may start reviewing the study when they are approached about participation. This will need further consideration as part of the work in combining the process with the HRA assessment and REC review, as the implementation of HRA Approval will require changes to current variable processes by both sponsors and sites.

7.8 Harmonising processes with devolved nations

There is agreement from the four nations group to implement a system which allows single reviews to be completed in all four nations and then shared between the nations. To get an operational system there may need to be further alignment on a common approach.

Discussions are currently ongoing with the four nations.

i. Options

1. Each nation organises to complete reviews for studies where it is the lead nation, within an agreed framework of reviews.
2. All four nations agree that reviews can be centrally allocated.

ii. Technical Assurance Team Recommendations

1. HRA Approval is designed to streamline research approval in the UK and to make the process easier for researchers and sponsors. Having one point of contact to centrally allocate the reviews will ensure that reviews are distributed fairly and will reduce confusion in the research community of who to contact. The HRA is currently including ECMC sites in the devolved nations in the project and the system is working well at the moment.
2. Technical Assurances Project Lead to coordinate a fixed-term compatibility review group including HRA staff and HRA Guardian, and representatives from Devolved Administrations.
3. UK Compatibility arrangements to be included in Technical Assurance draft SOPs for consideration by Technical Assurances Board.

7.9 Specialist Trusts

Over 90% of clinical trials in the NHS take place in Acute and Specialist Trusts, and the majority of support service funding received by pharmacy departments is also within

these Trusts. It is expected that a large majority of reviewers would come from these organisations.

Most of the remaining trials are split between Community/Primary Care settings and Mental Health settings. Pharmacy staff at the research-active Mental Health Trusts are able to provide relevant expertise and should therefore be able to be incorporated into the wider roll out. The HRA is currently working with the CRN and others to consider as part of cohort 2 of the HRA Approval roll out whether there is any value in implementing a Pharmacy Assurance process in Community/ Primary Care settings.

7.10 Studies not defined as CTIMPs

This is a heterogeneous group, some of which have protocols which specify the use of specific licensed drugs, other which involve food supplements or other administrations not licensed as medicinal products. It is not always clear from REC submissions alone if some studies would need pharmacy support. From a sample of records during 2014-15, the estimated number of studies in this category in a one year period is 30-50.

i. Technical Assurance Team Recommendation

Non-CTIMP studies involving pharmacy departments should be included in the Pharmacy Assurance process as part of HRA Approval as this is a small number of studies overall (see Appendix) that the system would be able to cope with without vastly increasing the number of reviewers required. This will further help to streamline research approvals in the UK.

Appendix

Projection of number and type of studies that would go through a pharmacy review process

Below data from samples of REC applications in HARP for new studies from period 1 April 2014 to 31 March 2015.

Studies defined as CTIMPs by the MHRA

Estimated new CTIMPs in NHS institutions during given one year period – 750

Setting

Estimated number taking place in acute/specialist trusts – 705 (94%)
Estimated number taking place in mental health settings – 25 (3.5%)
Estimated number taking place in primary care/community pharmacy – 20 (2.5%)

Type

Estimated number involving therapeutic use of IMP – 740 (98.5%)
Estimated number involving diagnostic use of IMP – 10 (1.5%)
Estimated number involving radioactive IMP – less than 10 (1%)
Estimated number involving IMP identified as ATIMP – less than 10 (<1%)

Breakdown by number of NHS sites

Estimated number with single NHS site – 235 (32%)
Estimated number with 2-4 NHS sites – 245 (33%)
Estimated number with 5-9 NHS sites – 170 (23%)
Estimated number with 10+ NHS sites – 100 (13%)

Breakdown of studies in Acute/Specialist setting by selected specialisms

Estimated number in non-oncology specialisms – 420 (60% of Acute/Specialist)
Estimated number in all oncology (including malignant Haematology) – 285 (40% of Acute/Specialist)
Of which:
Estimated number in malignant haematology alone – 75 (11% of Acute/Specialist)
Estimated number including paediatric patients – 75 (11% of Acute/Specialist)

Summary

The estimated maximum number of studies projected to go through the process is 800 per year. Of these a large majority take place in Acute or Specialist Trusts. Around one-third of the studies are single-site.

Document Control

Change Record

Version Status	Date of Change	Reason for Change
V 0.1 DRAFT	01/06/2015	First draft
V 0.2 DRAFT	01/07/2015	Reformatting, and rewording
V 0.3 DRAFT	10/07/2015	Insertion of recommendations section
V 0.4 DRAFT	22/07/2015	Changes suggested and incorporated by Head of Collaboration and Development
V 0.5 DRAFT	07/08/2015	Changes suggested and incorporated by Director of Systems and Development, reformatting
V 0.6 DRAFT	08/08/2015	Proof-reading and final editing
V 0.7 DRAFT	10/08/2015	Removal of unclear information
V 0.8 DRAFT	03/09/2015	Changes requested by CRUK, clarification of Appendix data source
V 1.0 FINAL	03/09/2015	Final

Reviewers

Name	Position	Version Reviewed
Jonathan Fennelly-Barnwell	Head of Collaboration and Development	0.3
Janet Messer	Director of Systems and Development	0.4, 0.5
Mary Cubitt	Programme Implementation Manager – HRA Approval	0.6, 0.7
Chris Cannaby	Head of Assessment and Assurance	0.8

Distribution of Approved Version

Name of person or group	Position	Version Released
HRA Approval Programme Board		1.0