Phase I Advisory Group
Minutes
30 June 2015
11:00 - 14:00

Present

Richard Tiner	Chair	RT
Catherine Blewett	Health Research Authority	CBl
Joan Kirkbride	Health Research Authority	JK
Charlotte Allen	Health Research Authority	CAll
Clive Collett	Health Research Authority	CC
Malcolm Boyce	HMR	MB
Ben Grey	Quintiles	BG
Simon Lee	Quotient Clinical & CCRA	SL
Joanne Slee	Quotient Clinical	JSl
Jorg Taubel	Richmond Pharmacology	JT
Keith Berelowizt	Richmond Pharmacology	KB
Christiane Abouzeid	BIA	CA
Steffan Stringer	AHPPI	SS
Nathan McCavery	AHPPI	NM
Jennifer Martin	MHRA	JM
John Sheridan	Chair Berkshire B REC	JS
Stephanie Ellis	Chair Hampstead REC	SE
Kath Osborne	REC Manager GM Central	KO
Ashley Totenhofer	REC Manager Bloomsbury REC	AT
Raj Bains	Chair Oxford A REC	RB
Adrian Baillie	Chair Surrey REC	AB
John Poland	ACRO	JP
Susan Sandler	ACRO	SSa

Apologies

Item	Item details	Action
1.	**Apologies:** David Carpenter, Deidre McCollam, Gary Johnston, Noel Landsman, Liz Allen, Anita Chhabra, David Carpenter, Deidre McCollum, Gary Johnston, Ian Skidmore, John Keen, Noel Landsman, Ulrike Lorch, Roger Rawbone	
2.	**Minutes of previous meeting on:** 10 February 2015 The minutes were agreed as an accurate record with the following clarifications being recorded in the minutes of this meeting. • Clarify regarding the tax threshold in response to the statement below. *It was noted that participation in a clinical trial does affect tax and benefits and is considered to be taxable earnings.*	

	The following statement is taken from the HMR&C website http://www.hmrc.gov.uk/manuals/eimanual/EIM71105.htm 'There will be no tax or NIC liability arising on the individual if the sums received do no more than reimburse the individual's reasonable costs of participating in the trial or research, including costs of travel and subsistence. However should the sums paid exceed those reasonable expenses then the excess may fall to be chargeable to tax as Miscellaneous Income, potentially giving rise to personal tax liabilities of the individuals which should be notified to the Inland Revenue under Self Assessment.' RT reminded the group that the minutes would be published on the HRA website after 2 weeks and that any requests for ratification should be made to CB within this period. Actions arising from the meeting - JM to communicate with Phase 1 accredited units to request feedback on registration deferral to support the position that a deferral mechanism should be in place for the EU CT regs. JM confirmed that this had been done. - CB to Review geographical location and whether commercial or non commercial for sponsors where registration could not be found. CB informed the group that this work had been undertaken as part of the overall audit on clinical trial registration which was being undertaken. The findings from this audit would be presented to the Board in September and would be available to the group after this time. -JM to identify the number of Phase 1 trials in open recruitment JM fed back to the group that this had proved more difficult than had been hoped or expected due to there being very large numbers returned when the search was undertaken on the database. The reason for this was that if the end of trial has not been declared then the trial may have ended but the database doesn't identify this. Additionally the way the trials have sometimes been recorded is an issue if they have not been accurately described and defined as HV Phase 1. To accurately identify which are Phase 1 HV involved looking into each individual record which would be significantly time consuming. AB suggested that this was important information to ascertain the issue and that the work to do this would be worthwhile. - CA confirmed she had sent out a communication to REC Chairs regarding what is expected when a document has been reviewed by a different REC. - CB to look at the reasons for provisional opinion reasons for Phase 1 clinical trials. CB confirmed that a review had been undertaken during the period 1.1.15 - 31.5.15. The most common reasons identified were - Changes to PIS - Changes to consent form	CB

	- Clarification on the dosing decisions. - Request for the correspondence with the MHRA - Clarification about the inclusion/exclusion criteria - Clarifications about the expenses procedure. - Concerns about insurance/liability - Request for supporting documentation e.g advertising information CB stated that further work would be undertaken to look at which issues could reasonably be picked up by the REC administration staff and highlighted to applicants in advance of the meeting. CB went on to inform the group that a REC Application Review and Advice (ARA) service was being rolled out to all CTIMPs over the upcoming months. This service involves a detailed review of the application to identify any issues which the REC are likely to request further information or clarification on and give the applicant an opportunity to provide this information in advance of the meeting. - CA TOPS specification, CA confirmed that she had submitted a change request to the developers for the following updates to TOPS. ➢ To be able to enter the exact long term follow-up date as opposed to selecting the number of months from a drop down menu. ➢ Entries with the monoclonal antibody box ticked should be displayed more prominently in the volunteers' history e.g. highlighted in red ➢ A message should appear when the user has been timed out. - CB to send the link to the Phase 1 section of the HRA website. CB confirmed that she sent the link after the last meeting and that some very helpful suggested changes had been received from KB and JM. These amendments had been made and the link had now been redistributed with the meeting agenda. http://www.hra.nhs.uk/resources/before-you-apply/types-of-study/phase-i-trials/	
3.	**Matters Arising** 3.1 Terms of Reference. RT informed the group that the minor changes requested at the last meeting had now been added to the ToR and also brought the groups attention to an additional section which had also been added. The HRA have added a standard statement to all ToR to say that if a member of the group would like to record the proceedings of the meeting, they must ask the permission of those present at the meeting and the fact that the meeting was recorded should be recorded in the meeting minutes. 3.2 REC workshop regarding transparency. CB agreed to request summary of the outcome of this event from Tom Smith. 3.3 Registration compliance audit. CB informed the group that this was an ongoing piece of work which would be presented to the HRA Board in September and made available after this time. CB confirmed that she had looked at the 70+ trials previously identified as not registered and where no formal deferral was in	

	place and about half have now registered and half remained unregistered and without an agreed deferral. 3.4 Monoclonal antibodies and the outcome of the meeting highlighted by Peter Dewland. NM informed the group that there was no update at that time but that he would chase up and feedback out of session. 3.5 Travel Insurance. CC informed the group that the ABI meeting had been postponed for a second time so there was no further development at this stage. The ABI are of the opinion that their guidance is clear. RT asked the CRO representatives how much of an issue this was in practice. The consensus was that this was not an issue that came up often.	
4.	**Update on the Clinical Trials Regulations** CB read out an update which had been provided by Sue Bourne. 1. EU Portal/Database development – led by European Medicines Agency (EMA) The EMA's work on the EU Portal and Database continues to be the main area of work. As previously noted, the readiness of these systems is very likely to be the determinant of when the Regulation will take effect as the Regulation stipulates that it will not be implemented until the EU portal and database are fully functional (references - Article 82 and Article 99). The EMA have stated that they will provide information on the predicted timelines for the EU Portal and Database in mid-2015; we therefore expect clarification on when the Regulation is likely to apply to be available by the end of July 2015. The EMA has focussed on 2 areas of activity in recent months: a) Completing work on business requirements, process maps and developing 'use cases' – the EMA had established several groups to work on these detailed aspects. The first part of 2015 was used to bring together the work of these groups and reconfigure the groups so there are fewer in number with fewer participants. These reconfigured groups have met frequently since April and it is reported that they have made good progress. It is expected that the detailed requirements will be complete by end of July 2015 – completion of this aspect is key to EMA setting out the timeline for completion of delivery of EU Portal and EU Database noted above. Specification of use cases is expected to continue for remainder of 2015. b) Transparency rules – The intention is to agree the rules that will meet the transparency requirements as set out in the Regulation and allow for automation of processes. As indicated in the previous update to the Advisory Group, the EMA held a public consultation on this issue at the start of 2015. Since this consultation, the EMA have published an addendum to the EU Portal and EU Database Specification (this is available on the EMA website); this addendum sets out functional requirements to enable the implementation of the rules; the rules themselves are still to be agreed. EMA provided a broad update at the regular stakeholder meetings (25 Feb and 12 May) and then they held a series of meetings with stakeholder groups during first half of June to discuss proposals for rules. They have	

	also received further written submissions from a number of Member States and stakeholders. It is understood that one of the key points under debate is around the rules for Phase 1 trials. The aim is to have the transparency rules agreed by the EMA Management Board in October 2015. 2. EU Commission Guideline – lay person summary of results In April it was agreed that the UK will lead development of a European Guideline on the lay person summary of results. This guideline will support Annex V of the Regulation. Amanda Hunn (HRA) is leading on this work and is establishing a small group that will support development of the guideline. The aim is to produce an initial draft for November 2015. The EU guideline will be reviewed and agreed by the European Commission and Member States before it is finalised and published. The EU Commission and Member States have also discussed the need for other guidelines and FAQs to support the Regulation.	
5.	**EMA update on transparency** MB updated the group with the following • Trials have been categorised as shown in the EMA presentation which was distributed to the group. Category 1 includes non-therapeutic trials in healthy volunteers and patients - registration details of those trials will not be published until one year after the end of the trial. • The EMA still plans to publish the summary trials results one year after the end of the trial: that deadline is seen as a 'red line' by the legislator, who wants no erosion of the principle that results will be published in 12 months. Stakeholders expressed concern about the threat to Phase 1 in Europe specifically linked to the issue of patent application and were keen to extend the timeframe to 24 months. There was also discussion about the definition of the end of trial. The Regulation states that it should be last subject last visit or at a later date as defined in the protocol, but does not clarify that further. There were suggestions that the end of trial could be defined as completion of the analyses, but also concern that different Member States might have different opinions on whether that is acceptable. • The EMA is currently proposing a delay of only 5 years to publication of trial, and product specific documents submitted as part of a clinical trial application for category 1 trials. Up to 9 years had been proposed in the consultation. Stakeholders made a counterproposal that publication be delayed until 7 years after the end of the study. • The Regulation does not differentiate between trial specific and routine inspections, so all will be published, after the inspected party has responded to the findings. • Serious breaches will be published after the MS has reached a conclusion. The sponsor and MS will provide summaries for publication. • Owing to the transparency requirements, some trial documents will	

	have to be written differently, e.g much less information in the protocol about the background of the IMP, no CMC details in the Investigator Brochure and fewer signatories on the trial report. • Stakeholders repeatedly expressed concern about the impact of the proposals on Phase 1 in Europe, and particularly about the perception of the changes by sponsors outside of Europe. The EMA asked for written feedback by 12 June 2015 giving examples supporting a case for extending the proposed timeframes for publication of results and documents. No further meetings with industry stakeholders are planned. The EMA, MS and European Commission will revise and agree the rules on transparency , which will be submitted for endorsement in the October 2015 Management Board. RT asked whether the option of requesting a deferral had been taken forward by the EMA and MB referred to page 18 of the slides which had been distributed with the meeting agenda, saying that this had largely been rejected. MB further suggested that there was a concern that different members states would interpret the definition of the end of study in the protocol differently and that the interpretation of the end of study may not always be truly accurate to allow more time before the requirement to publish. It was noted that not all Member States run Phase 1 trials and these Member States aren't therefore engaging with this issue. The Member States which run Phase 1 trials are all united on this issue but the number is relatively low. It was stated that the major pharmaceutical companies have requested no publication and these companies often have large patent departments. However, only about 10% of new molecules coming through are coming from the large companies, the other 90% are coming from small to medium companies and academia. MB stated that the EMA have said that they have consulted a patent lawyer but the advice does not appear to be in keeping with what is expected when applying for a patent. The EMA have requested real life examples of when it has not been possible to get a patent due to information being in the public domain. MB suggested that the UK had regained some work since the introduction of the Directive but this issue would lead to a setback. SL suggested that it would have an adverse effect on small and medium sized companies wanting to undertake further development in the EU. JT noted that the legislation was very clear about the 12 months but there is a feeling that putting information in the public domain within this period offers no real benefit but is likely to result in sponsors placing more work in the US as they will not be impressed by any suggestion of not being clear about the end of trial definition in the protocol. JS referred to the suggestion that the requirement to have information in the public domain 12 months after the end of the trial may result in the end of trial definition being inaccurate and asked what RECs should do when there is a concern that this has occurred. It was agreed that it would be the responsibility of the REC to request further clarification or justification for the description and ultimately decide on whether it is ethical. JM added that the MHRA have previously given findings when they	

	have identified that the end of trial description is not in accordance with guidelines, for example when it is described as when the database is closed down. The sponsor would have to be able to justify why this was deemed to be the end of trial. This could potentially have EU wide implications if there are differing practices and standards. RT asked whether Phase 1 clinical trials being in category 1 would make a difference to which MB said that this was unlikely, suggesting that there is complete agreement regarding publication of data from later phase trials but the only benefit for publication of Phase 1 trials is to competitors. MB added that only 1 in 10 compounds which reach Phase 1 trials go on to reach the market. MB referred to the patent requirements and said that based on unpublished data, anything which is pre published is considered to be prior art. The inventor then has 12 months to collect information and should publish 6 months after that. The inventor can make amendments but if there is a substantial change, a new application would need to be submitted and the priority date resets. MB suggested that publication of the clinical trial data within 12 months breaches 2 of these standards. Work between the Phase 1 community and the MHRA has been positive and we all needed to work together in regard to the 12 months rule. RT said that he had previously had contact with the Newport patent office and they had been extremely helpful. MD confirmed that they had already spoken with patent lawyers regarding the issue. RT noted that further information about the requirements of publication should be known after the management meeting in October. CA said that she had attended the EMA meeting to discuss transparency and added that various stakeholders had been represented. The positive side was that it was agreed that category 1 would also include Phase 1 in patients as well as healthy volunteers which was a positive development. Some early clinical trials would fall into category 2, where there is an assessment of efficacy, and will require greater protection. For Phase 1 there may be a reconsideration of the 12 month period if good examples are submitted as case studies. However, the EMA are not willing to make a policy change based on anecdotal information. Some comments have been submitted. The IMPD quality section is the only paperwork not to be published under the current proposal. The importance of submitting examples to be used as case studies was noted as it is not reasonable to complain about an issue and then not provide the information to justify the position. Sponsors will have this information and should be encouraged to share it. JS asked what the HRA position is on these particular issue to which JK responded that the MHRA are taking the UK lead on the policy negotiations but the HRA are feeding in. It was suggested that it would be important to encourage sponsors to submit examples and also to work with other Member States to get them on board. MB suggested that it may be difficult to get industry and academia on board with this although it will affect them.	

	RT suggested that the process for requesting a deferral appears to work well. SL added that Quotient Clinical keep metrics on deferral requests and the majority of their work is from outside the EU and the majority of sponsors do request a deferral. JT suggested that the issue about deferral made people aware that it is an issue which will affect them. If sponsors are placing a trial in the UK they are also making a commitment to publish, with or without a deferral, which could cause an issue later down the line that will then need to be justified. CA suggested that the discussion at the EMA meetings implied that they have the legislation which needs to be implemented and they are working out how best to do this but are also mindful of the need to ensure that the EU continues to be an attractive place to run early phase clinical trials. SL said that they had been in contact with the Secretary of State for Business and Innovation. It was suggested that this may be a useful conversation to have as sometimes it is not clear what the actual impact will be in real terms. AB suggested that if this legislation can't change then maybe something can be done about the patent legislation. It was however noted that the patent legislation was far more broad than just Pharmaceuticals so this was unlikely. It was noted that the largest growing nations for Phase 1 clinical trials are currently Australia and New Zealand. CA asked whether the outcome of the judicial review would affect this issue. RT said that he was limited in what could be said in relation to the judicial review at this time. The court hearing has been set for 16 July 2015 and only information which is already in the public domain can be referred to. RT read a statement which had been prepared by the HRA. "We can confirm that the claimant has been granted permission to proceed in its application for judicial review, although not in respect of all its grounds of claim. Sense About Science have also announced that they have applied to be an interested party. We would point out that the merits of the claim are not considered at permission stage. The issue of merit will be considered at the substantive hearing. The HRA has filed detailed grounds of defence, and will continue to act in line with its statutory duties and responsibility to protect and promote the interests of patients and the public in health research." RT added that there had also recently been an article in the British Medical Journal the week beginning 22 June 2015. http://www.bmj.com/content/350/bmj.h3428 MB asked what the impact would be should the complainant be successful, particularly in regard to the CT Regulations. It was confirmed that the judicial review will have no impact on the CT Regulations, just the interim provisions put in place by the HRA. JT added that from the complainant's perspective, it is a point of law. The actions are not perceived as lawful, it is not about transparency in itself, adding that the complainant publishes more clinical trials than its competitors. If the complainant is successful in their claim then the HRA will have to rethink their policy. RT added that it	

	was unlikely that there would be a response on the date of the court case as these things often take some time to complete.	
6.	**Generic Screening documentation - Update** CAll thanked the group for the comments added to the generic screening document which had been distributed. These comments had been incorporated into the document but unfortunately the updated document had not been distributed in advance of the meeting. This version would be sent to the group with the minutes of the meeting. KB suggested that there are some tests which he is not sure should be included although was in favour of the shortened version of the document. Some of the suggested GP tests would not happen in a GP surgery. The document needs to be broad to cover wide ranging clinical trials but some of the tests do appear to push the boundaries. Examples of these were ECG and echocardiogram and also it was agreed that X-rays for generic screening would not be appropriate as they would be considered a research exposure so would require ethical review under the Ionising Radiation (Medical Exposure) Regulations (IRMER). CAll clarified that all of the tests which are listed in the generic document have been included in previously used documents from various organisations. The point of the document was that it was broad and allowed the organisation to select the tests which are relevant to that organisation. JM added that if these tests have been included in REC approved documentation then there could be an impact if there is now agreement that they would not be appropriate. AB suggested that if the generic document means that individual documents are not required to be reviewed by a REC then the generic document should also include comprehensive information about the possible risks. This could possibly be in another document which details the higher risk. The group discussed whether X-rays, EEGs and Echo cardiogram should be part of pre screening. It was agreed that X-rays would not be appropriate due to the regulatory requirements and that this should be removed from the generic document. The group agreed that whilst EEG would be rare, the risks and burden of this test were minimal. It was agreed that this could remain in the generic document as some sites may require this test for some trials. The group agreed that an echo cardiogram would not be considered risky or burdensome but as they are unlikely to be undertaken on site, it should be made clear that there is a possibility that the participant may have to travel for this test. AB suggested that the wording regarding the exercise stress test did not adequately describe the risks and burdens of this test. MB said that they had opted out of the work looking at developing a single generic template as they have always submitted generic documents to a REC for review and if they change them then they just submit to the REC	**CB**

	again. KB added that they do not undertake generic screening but were of the opinion that any generic documentation would need to be comprehensive. Updates to be made -Further information about sputum testing -Remove X-ray -More information about the risks and burdens of exercise stress test -ECG - may require referral elsewhere for this test. -Include a general line about what happens if any significant findings are identified from any tests. CAll thanked the group for their input and explained that there will be guidance on how to use the document which will be provided when the template is published. RT said that he had something that he was going to raise as 'any other business' but would raise at this point in the meeting as it was in relation to non study specific recruitment and advertising. An article had been published in the Journal of Medical Ethics. ABSTRACT Pre-recruitment is the practice of recruiting potential participants to a list of potential research volunteers in general rather than to a specific research project. This is a relatively common practice in commercial medical research as it reduces the time and hence costs of recruitment and makes it possible to be more efficient by recruiting participants who may be useful for a variety of different pieces of research. It focuses on present practices in the UK although the conclusions and suggestions should be read more widely than this, applying in any situation where pre-recruitment is used as a recruitment tool for clinical trials and beyond. Current pre-recruitment practices in the UK clash significantly with what are seen as best practices and ethical guidance with regard to recruiting participants to individual trials, and insofar as this undermines these practices should be reformed. RT noted that there were errors with the information included in the article and that some information was out of date. The HRA were currently looking at how they could respond. JK reiterated that it was a poorly researched paper which was out of date. The HRA does have a process in place for the review of generic advertising of Phase 1 clinical trials. A response would be drafted and submitted to the JME to set out the current position. JK asked whether there were similar processes in other countries to which SL replied that he was unsure but would try to find out.	**CAll**
7.	**Phase I Management Information Data** CB informed the group that the management information for the period October 14 to March 15 had been distributed along with some guidance	

	explaining the significance of the reported time periods. JK noted that the MI data suggested that the review timelines were getting shorter which was positive. However, the service had been struggling due to staffing issues caused by REC staffing taking up positions in the HRA Approval programme team. The REC service was currently on the limit of what is possible to maintain the current timelines. JK asked those present to highlight any problems which are experienced as it may be necessary for intervention to ensure that timelines are not adversely impacted. JK added that UKECA have requested data to ensure that RECs review sufficient CTIMPs. This information will be considered in relation to reviewing the recognised status of any RECs reviewing too few CTIMPs in a year. It is hoped that the service will however retain the same number of Phase 1 RECs as previously requested by this group.	
8.	**Any other business** 8.1 DupCheck - KB KB said that the topic of preventing over-volunteering had been around for a while but there had been a shift to moving towards a more centralised European system. KB had been made aware of a system called DupCheck which could possibly link the current UK system with a Europe wide system. The EMA have been consulted and they have said that they like the system. It is a paid system with a nominal fee and is favoured by Pharmaceutical companies and CROs so that volunteers can be identified when they cross EU borders. KB suggested that it would be worthwhile looking into how the DupCheck system could work with TOPS and whether the systems could link up. CB agreed to send a link to the DupCheck site with the minutes. CB added that she had spoken with a representative of DupCheck who had said that he had already had discussions with KB. There had been an intention for a while now to look at how TOPS could link up with a European system and the HRA were happy to have discussion about how this could be achieved. However, it was also noted that there were significant limitations with regards to systems development at this time due to the significant developer time required to implement the HRA Approval requirements; which is a HRA priority. CB added that this particular system would require changes to their practice as it was different data fields being collected.	CB
9.	**Date of the next meeting** 9 February 2015 11:00 -14:00 Skipton House (followed by lunch)	