NHS
Health Research Authority

Phase I Advisory Group
Minutes

Date: 9 February 2016

Time: 11:00 - 14:00

Venue: Skipton House - Room 1
80 London Road
London
SE1 6LH

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Present

Richard Tiner	Chair	RT
Charlotte Allen	Health Research Authority	CAll
Nicola Burgess	Health Research Authority	NB
Joan Kirkbride	Health Research Authority	JK
Steffan Stringer	AHPPI	SS
Simon Lee	Quotient Bioresearch & CCRA	SL
Joanne Slee	Quotient Bioresearch	JS
Alastair Walker (by teleconference)	HSC REC A	AW
Clive Collett	Health Research Authority	CC
Odile Dewit	ABPI	OD
Christina Abouzeid	Bio-Industry Association	CA
Daryl Rees	Generic Document Review Committee	DR
Ian Skidmore	Cambridgeshire & Hertfordshire REC	IS
Margaret Jones	Riverside REC	MJ
John Poland	ACRO	JP
Malcolm Boyce	HMR	MB
Carl Phillips	Wales REC 1 and 2	CP
Ceri Edwards	Simbec	CE
Jan Downer	Harrow REC	JD
Keith Berelowitz	Richmond Pharmacology	KB
Jagjit Sidhu	Wales REC 1	JSid
Bill Davidson (for item 4 only)	Health Research Authority	BD
Stephanie Hill (for item 11 only)	Health Research Authority	SH

Item	Item details	Action
1.	**Apologies:** Jennifer Martin, John Sheridan , Ulrike Lorch, Deirdre McCollam, Alan Reuben, Kath Osborne, Roger Rawbone, Christiane Abouzeid, Catherine Blewett, Susan Sandler.	
2.	**Minutes of previous meeting on 30th June 2015** The minutes were agreed as an accurate record with the following clarifications: • There were a number of duplications in the apologies list. • Paragraph 2 should be redacted.	
3.	**Matters Arising** <u>HRA Response to 'We could be heroes: ethical issues with the pre-recruitment of research participants' by D. Hunter</u> RT highlighted that the HRA had published a response to the article regarding pre-screening for clinical trials published by D.Hunter. The HRA had corrected and provided clarification to several of the concerns raised in the article. The response from the HRA was published in the Journal of Medical Ethics in December 2015. A further article from D.Hunter was published online in the Journal of Medical Ethics on 29th January 2016. The subsequent article thanked the HRA for providing the clarifications but raised some further concerns such as the issue of paying volunteers to recommend a friend to participate in further clinical trials. <u>REC Applications – Provision of pre-meeting advice (page 3 of previous minutes)</u> JK informed the group that the process of providing advice to applicants prior to the REC meeting was no longer called the 'REC Application Review and Advice Service' although the function would still be offered to Phase I studies. SL stated that he had experienced this service and found it very helpful. <u>Recognition of RECs (page 11 of previous minutes)</u> JK stated that UKECA had agreed to maintain the recognition for each of the current RECs which reviewed CTIMPs however, the number of recognised RECs would be reviewed again this month. JK was unsure what UKECA would decide as some RECs had only reviewed one CTIMP in the last year. JK highlighted that reducing the number of recognised RECs	

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	could potentially cause problems in the future depending on what the requirements set out in the new Regulations will be. JK questioned whether the group was concerned that some RECs only reviewed one CTIMP per year. There were no concerns raised by the group regarding this. JK stated that UKECA might decide to keep the number of recognised RECs but to remove some of the Phase I flags. <u>Dates for next Phase 1 Advisory Group meeting</u> CAll would check the dates of the Phase 1 REC meetings in order to avoid clashes with these meeting dates particularly for the RECs which meet on the second Tuesday of the month. The group expressed a preference for meeting in late July as opposed to early September.	CAll
4.	**UK Policy Framework for Health and Social Care Research** BD attended the meeting to provide an overview of the new UK Policy Framework for Health and Social Care Research which would replace the current Research Governance Framework when it was finalised. BD provided the following updates: • The HRA and the devolved administrations were developing a new UK Policy Framework for Health and Social Care Research to set out the high-level principles of good practice in the management and conduct of health and social care research in the UK, as well as the responsibilities that underpin high-quality ethical research. • The closing date for the consultation is 24th March. The group was invited to respond to the online survey. • Members of the group were invited to attend the workshop for commercial funders and sponsors which was being held on 3rd March in London. • The consultation was progressing well in terms of the number of comments received so far. BD welcomed suggestions for improvements and constructive criticisms to ensure that the Framework was robust. RT invited the group to send any comments or suggestions for improvements to CAll by 1st March in order that a joint response from the P1AG could be prepared. RT asked members whether they thought that the Framework would help to attract research to the UK. OD considered that if it supported infrastructure and Chief Investigators then it should help to encourage research. It was questioned whether the new Regulation or an EU	CAll

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	Referendum would affect the Framework. BD stated that the document was very high level and needed to be applicable to all research types therefore, it was not specific regarding the new Regulation but would need to be compatible. BD stated that the document had been developed during the time of the Scottish independence referendum and therefore, the effect of an EU referendum would be limited.	
5.	**EU Clinical Trials Regulations** <u>CAll provided the following update on behalf of Sue Bourne, Head of Guidance & Advice</u> An essential component of implementing the new arrangements set out in the EU Clinical Trial Regulation would be the dedicated IT infrastructure (the 'EU portal' and 'EU database'), which the European Medicines Agency (EMA) must set up and maintain. The timing of the application of the Regulation had been made dependent on the EU portal and EU database being confirmed as fully functional through an independent audit. The actual date when the Regulation would become applicable would be six months after the European Commission publishes the notice in the Official Journal of the European Union (OJEU) confirming the IT infrastructure is fully functional. In October 2015, the EMA published their anticipated timelines for the development of the IT infrastructure and thus the expected date of application of the Regulation (at that time it was set out as December 2017). Following a discussion at the EMA's Management Board in December 2015 the previously announced timelines have been revised and new dates published. The new timeline anticipates that: - The EU Portal and EU Database will be available for independent audit by August 2017; - The European Commission will publish the notice in the Official Journal of the European Union in March 2018 (assuming that the independent audit confirms that EU Portal and EU Database are fully functional); - The Regulation will become applicable by October 2018 In publishing these revised timelines, the EMA have stated 'this is the maximum timeframe and every effort will be made to shorten it and bring the Regulation into operation as soon as possible'. The HRA, Quotient Bioresearch, ACRO and Richmond Pharmacology confirmed that they would all be involved in the User Acceptance Testing.	

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	JS questioned whether it would be possible to explore piloting the process between RECs and Phase I units in order to test how things would work and that timelines would not be affected. MB questioned whether the HRA and MHRA would have the freedom to keep their timelines with the new system. JK confirmed that a meeting had been set up at the end of this month to re-visit the practical implementation of the new process between the MHRA and HRA. <u>Lay Summary of Results</u> RT provided the following update regarding the lay summary of results work which was being led by Amanda Hunn, Engagement & Policy Manager: The HRA sent a draft of the guidelines to the European Commission (EC) in November and received comments back in late December. The HRA then sent a revised draft back for mid-January. This would go to the ad-hoc working group for clinical trials at the EC on 8th Feb. If the EC is happy with that draft, it would then be sent for formal consultation which would last three months. The feedback will be provided to the HRA and the taskforce for further revision later this year.	
6.	**Transparency in Phase 1 research** <u>European Disclosure rules</u> RT stated that the European Disclosure rules had been released which specified that in the EU, a sponsor may opt to defer the publication of the final summary of results and the layperson summary for a maximum period of 30 months after the end of the trial. Other study documents would be made public up to a maximum of 7 years after the end of the trial. SS questioned whether the HRA would apply the same criteria. CAll would check with Janet Wisely. MB praised the group on the collaboration and team effort which had gone into the publication consultation and had appreciated the input from the MHRA and HRA. **Post Meeting Note:** *Janet Wisely confirmed the following: 'The HRA will align requirements. It may be that the HRA will encourage more transparency but we would not expect to have different requirements. The requirements will be imposed through the regulations and UK legislation'* <u>Registration audit - Phase 1 outcome</u> NB provided an overview of the registration audit data. RT noted that out of 325 trials in the reporting period, 77% had been registered on a publicly accessible database and 15%	Standing item CAll

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	had been granted a deferral. <u>Risks of Phase 1 research with healthy participants: A systematic review</u> The conclusion of the review of 475 trials was that Phase 1 trials may cause moderate or low harm but not severe harm and that increased transparency should be encouraged. RT noted that only one of the authors of the paper worked in the UK therefore, many of the points were not relevant. CC would monitor whether there were any further responses to this article. <u>Biotrial</u> The group noted that in January 2016, one person had died and five more had been hospitalised during a Phase I clinical trial in France. The group would monitor any recommendations which were made following the full investigation which might affect Phase I trials in the UK.	CC
7.	**Generic Screening documentation** <u>Generic Document Review Committee - Policy and Procedure for information and approval</u> NB introduced the Policy and Procedure for the Generic Document Review Committee and invited comments from the group. The document was approved subject to the following changes: • There was a section missing from the 'Scope' section in paragraph 2. • Item 4 should specify the timeline for when the notification would be sent. • References to giving an opinion should be removed in order that this was not confused with giving an ethical opinion. • Section 4.4 should specify how the HRA liaises with a particular company when a concern is raised. JK highlighted that although the HRA was looking for new members to join the Committee, it was still important to keep the numbers small (a maximum of 6) in order to ensure consistency. JK stated that it would be helpful to agree a wording for the adverts to specify who had approved them (e.g. approved by the Generic Document Review Committee). It was highlighted that it might be difficult to include this is in some adverts due to the amount of text allowed. KB stated that each document reviewed by the Committee was allocated a reference number and therefore, this reference number could be included in the	

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	footer or the advert in order to demonstrate that it had been reviewed. KB stated that interactions with the generic group had given a fast turnaround and had made things much easier. CAll introduced the Generic Screening Template and supporting guidance and invited comments from the group. The documents were approved subject to the following changes: • Some concerns were raised regarding the inclusion of Sputum Induction as this potentially broadened the scope of the document beyond generic screening however, a number of CROs had asked for this to be included. It was agreed that some information regarding the side effects of Salbutamol should be included. It was agreed that supporting rationale should be included if a unit wanted to include a sputum induction or skin prick test as part of generic screening. • It was considered that information regarding travel expenses should be included e.g. an option to use if there is or isn't going to be any payment of travel expenses. • The term 'slit lamp' should be replaced with 'light'. • An explanation of measuring fluid level inside of the eye should be provided to state that this just involves a puff of air. • The guidance should be more explicit that it is not mandatory to use the template and that the template is designed to be a supportive document rather than a mandatory document. • The guidance should state that the tests which are not being used should be deleted from the list rather than using tick boxes. CAll would action the above changes and arrange for the documents to be published on the HRA website	CAll
8.	**Phase 1 Advert Guidance re Payment** The group was asked to consider the following questions which had been received regarding generic advertising for Phase 1 studies. 1. *One of the ideas we were considering was rather than use a payment of 'up to £100 per day' if we would be able to use wording to the effect of 'Last year our volunteers received an average of £xxx on our paid clinical trials'" - Would this be considered acceptable?*	

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	The group considered that this was not acceptable. It was suggested that a better approach would be to state that volunteers could receive up to £100 per day with a link to the website. For example, '*You would receive up to £100 per day. For further information regarding payments for previous studies please view our website……'* 2. *Is the figure £100 per day still appropriate?* It was noted that this figure was based on the National Minimum Wage however, the term 'living wage' tended to be used more frequently now. DR stated that the national living wage was £9.70 per hour. KB noted that this would make £272 a day for a 24 hour period, and £72 for an 8 hour day. IS stated that the amount should be a minimum of £100 per day for a 24 hour period of residence. The group agreed that individual companies could choose to offer more than £100 as the minimum if that is what they usually do however, £100 should remain as the recommended minimum for a 24 hour period. 3. *Examples of adverts have been sent to the HRA where the amount is at the bottom of the text section but in a font which is larger than the other text and examples where the amount is in the middle of the advert, the same size font but is in red where the other text is black. Would this be considered prominent?* It was agreed that this was difficult to specify as it would depend on the advertisement. The group acknowledged that the majority of people reading the advert would be looking for the figure. CC asked about pay per click adverts (e.g. the sponsored search results on Google, Bing, Yahoo etc.) as these are not reviewed by an ethics committee and the links can direct users to trials which pay less than the advertised amount. It was discussed that if this type of advert was study specific, the method of advertising should be mentioned in the application form and a copy of the advert provided with the submission. DR noted that generic pay per click adverts had never been submitted to the Generic Document Review Committee. It was agreed that the HRA website should be updated to specify that generic pay per click adverts must be submitted to the Generic Document Review Committee. Pay per click adverts should also be referenced in the Generic Review policy & procedure as an example of the types of documents which must be submitted.	Catherine Blewett
9.	**The Over volunteering Prevention System (TOPS)** CAll provided the following updates regarding the TOPS audit:	

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	An audit of TOPS was commissioned as part of the HRA's 2014/15 internal audit plan, to determine whether the current HRA data security and data quality processes and controls surrounding the TOPS website enabled research participant data to be held securely and confidentially whilst maintaining its integrity. The scope of the review focused on assessing the adequacy of the policies, procedures and controls which had been put in place by the HRA to ensure the security and ongoing quality of the data maintained within TOPS. The assessment also included a review of the data migration controls utilised as part of the implementation of the new TOPS website. CAll explained that some TOPS users had been interviewed as part of the audit and thanked those who had participated. CAll stated that the audit had received a good outcome with the following recommendations: i. It was recommended that **the** HRA re-issued the user manual to TOPS users to ensure that users were all aware of the available functionality within the new website. The user manual was re-issued to TOPS site admin users on 25/11/2015 **ii.** The HRA should issue guidance to users to highlight where processes have changed or been added as a result of the new website being implemented e.g. new user process and change to record process. **iii.** The HRA TOPS team should liaise with the HRA IT team to implement a regular 'IT and cyber security risks and threat' communication that can subsequently be distributed to CTUs for action, as required. CAll explained that it had been decided not to proceed with this recommendation as it had not been included as a recommendation in the audits of any other HRA systems. iv. The specific responsibilities of the HRA and the units which use TOPS should be clarified, specifically with regards to the data held on TOPS in relation to ownership, security, quality and maintenance. CAll asked the group whether they would be happy for the statement regarding responsibilities to appear on TOPS for a user to accept on their first login.	CAll

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	The group agreed that the statement could be added to TOPS with the following amendments: i. It should be possible for site admin to see whether a user has accepted the statement and on what date & time. ii. The statement should mention the requirement to update volunteer records in a timely manner. iii. The statement should make it clear that the security of the data in terms of what is being transmitted is the responsibility of the HRA. Ensuring there are secure systems in place in their unit, is the responsibility of the user.	
10.	**Phase 1 Management Information (MI) Data** The MI data was noted by the group. KB stated that it was useful to be able to send the information to sponsors as an indication of how long the ethical review process would take however, some studies seemed to have been omitted from the report. SS noted that the tabular information was useful however, it would be beneficial to include some graphs to show improvements overtime. It was commented that the website should provide a more up to date version of this report. JK highlighted that improving consistency would be a major focus for the Research Ethics Service next year and asked for any examples of inconsistencies. JK stated that the data did demonstrate a high number of provisional opinions for Phase I studies. KB highlighted that some RECs raised questions prior to the meeting which was useful and might help to reduce the number of provisional opinions. JK asked whether it would be possible for someone to write a study which could be used for a Phase I training exercise as the HRA could possibly pay for someone to do this if it was possible to find a volunteer before the end of the financial year.	Catherine Blewett
11.	**Any other business** 11.1. <u>HRA Transparency Forum</u> The group was asked to identify one member to represent the P1AG on the HRA Transparency Forum. SL stated that he might be attending in on behalf of the CCRA. It was not known whether the AHPPI were already represented on the forum. The group considered that the individual would need to be representing the P1AG and not anyone else.	

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	CAll would follow up with Catherine Blewett and Tom Smith to check whether there was any further information. 11.2. Ionising radiation risk statement. SE provided an overview of the document which had been produced from the radiation assurance project in order to standardise the way in which the level of risk was described on information sheets. The group agreed that this was a helpful document. 11.3. Paying to recommend a friend to participate in clinical trials. The London Bridge REC had asked for comments from the group on whether paying to recommend a friend to participate in a clinical trial was common practice and considered to be acceptable. DR stated that he was seeing this more and more frequently. SL stated that Quotient Bioresearch had been paying volunteers to recommend a friend for a number of years. DR stated that if the material was worded appropriately, the Generic Document Review group had been approving these documents. The group agreed that payment should not be based on the friend completing a study as volunteers should have the right to withdraw at any time. The group agreed that one or two referrals from the same volunteer was acceptable however, if any more referrals were received it was important to monitor to ensure that individuals were not making a small business from recommending people to participate in clinical trials. CC highlighted that some forms just required someone to enter an email address to recommend a friend so the person might not even know about it. It was agreed that this approach was not acceptable.	
11.	**Date of Next meeting** The date of the next meeting is to be confirmed. Post Meeting Note: The next meeting will be held on 27th July 2016	

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