Phase I Advisory Group

Minutes of the meeting held on 25 July 2013

11:00 - 13:00

Skipton House, London

In Attendance

Richard Tiner (Chair)		RT
Catherine Blewett	HRA	CBl
Joan Kirkbride	HRA	JK
Clive Collett	HRA	CC
Peter Dewland	AHPPI	PD
Dierdre McCollam	Bio-Kinetic	DM
Malcolm Boyce	Hammersmith Medicines Research	MB
C Brearly	ABPI Experimental Medicines Group	CB
Simon Lee	Quotient Bioresearch	SL
Rachel Bacon	Quotient Bioresearch	RB
Ulrike Lorch	Richmond Pharmacology	UL
Keith Berelowitz	Richmond Pharmacology	KB
Jennifer Martin	MHRA	JM
John Sheridan	Berkshire B REC	JS
Anita Chhabra	Cambridge Central REC	AC
Hilary Russell	HSC REC 3	HR
John Keen	Brent REC	JKe
Stephanie Ellis	Hampstead REC	SE
Chris Vallins	Surrey Borders REC	CV
Alan Ruben	Westminster REC	AR
Susan Tonks	Berkshire REC	ST
Roger Rawbone	GM Central REC	RR
Kath Osborne	GM Central REC	KO
Ashley Totenhofer	Bloomsbury REC	AT
Ian Skidmore	Hatfield REC	IS
Stephen C	Quotient Bioresearch	SC
Noel Landsman	Quintiles	NL
Pooham Chowhary	Quintiles	PC

Item	Item details	Action
1.	**Apologies:** **Janet Wisely** **Sue Bourne** **Jan Downer** **Christina Abouzeid** **Art Tucker** **Peter Heasman** **David Carpenter** **Gary Johnston**	
2.	**Minutes of previous meeting on 8 February 2013** The minutes were agreed as an accurate record.	

3.	**Matters Arising**	
3.1	IS noted that he was listed as Vice Chair of the Welwyn REC and confirmed that this REC had now closed and it was now the Hatfield REC.	
3.2	9.2 Nuffield recommendation We note that, in its current guidance to the pharmaceutical industry, the ABPI provides advice against over-volunteering, recommending a 'washout period' between studies: in general this is of a minimum of three months but dependent on the compound being studied and its mode of action. However, concerns about 'over-volunteering' relate not just to the potential risks to the individual's health from the particular studies, but more subtly to the notion that 'loaning one's body' through first-in-human trials should not be regarded as a long-term low-paid job. One way of dealing with this wider concern about the nature of participation would be to restrict the total number of trials a person may ever participate in, regardless of 'washout' periods in between. We recommend that the National Research Ethics Service (NRES) should consult on the possibility of limiting the total number of first-in-human trials in which any one individual should take part." RT stated that they had been approved and agreed by The National Research Ethics Advisory Panel (NREAP) at their meeting on 27 March 2013. RT asked those present to look at the recommendation which had been made and take them back to their respective organisations so that similar & universal language was being used and definitions were understood.	
3.3	15. Terms of Reference CC stated that he had now revised these and had hoped to bring to this meeting for formal approval. It was agreed that they would not require formal approval but should be circulated to all members of the group	**CC**
3.4	9.1 - TOPS JK stated that the legal transfer of TOPS has now been completed. With effect from Monday 22 July 2013, TOPS has come under the remit of the Operations Directorate.	
3.5	10. Improvements JK confirmed that all of the improvements which were agreed at the last meeting have now been implemented. JK added that there had been an initial problem with an early submission which was not valid on receipt and was therefore not accepted but others seem to have worked well.	
4.	**Payment to participants in Phase I trials**	
4.1	RT stated that the agreed statement was taken to the NREAP meeting on 27 March 2013 and was well received by the panel who have now approved it. CC confirmed that this was now in place. CC explained that the panel are looking at guidance and how best to consult on	

	this. The statement was now accepted and endorsed by the panel. RT added that there was an outstanding question regarding awards of luxury goods which they were waiting for the panel to provide guidance on, as well as any further issues. CC confirmed that the panel would discuss the issue of luxury goods and that he would bring the outcome of this back to the meeting, as well as any further issues.	**CC**
4.2	JS asked for discussion to clarify the position on payment to patients in Phase I trials. This was an issue which the REC would like clarified as it had been noted that there was an expectation that healthy volunteers are paid for their time and inconvenience when taking part in a Phase I clinical trial but this was not usually the case for patients, even though the time and inconvenience might be the same. The suggested reason for this was that patients are more altruistic than healthy volunteers who typically only take part for the payment and that payment to patients would be an unfair incentive. There was however a question around whether patients are in fact more altruistic than healthy volunteers and whether this is a fair assumption to make as altruism is not always the only reason for a patients taking part in a Phase I clinical trial. Patients may be inclined to take any opportunity to ease or improve their clinical condition, regardless of how minimal the likelihood. It was queried whether this issue referred to patients for whom the IMP is aimed as this was unusual in Phase I trials as there was no expectation of a benefit for the participant . The example of a patient with renal failure being used in a study which was looking at renal clearance so that poor renal function could be compared with normal renal function was discussed. It was agreed that it was necessary to clarify whether the patients are patients who have the condition for which the drug is being investigated or whether they are patients for whom the drug is not intended but they fit the inclusion criteria for the trial for other reasons. JK suggested that there may be some degree of administrative confusion regarding what is meant by a Phase I clinical trial. It was stated that a Phase I trial is a non therapeutic trial where there is no intended benefit to the participant However NRES used a description of trials involving first time use of a drug in patients, usually cancer studies as Phase 1 in patients, but the correct categorisation of such studies was a CTIMP. It was suggested that in terms of payment for this group of participants, they are subject to the same inconvenience as a healthy volunteer and should therefore receive the same payment for this. The group agreed that this was appropriate. Further discussion took place regarding whether the setting for the clinical trial, i.e hospital or Clinical Trial Unit should make a difference. IS further queried whether there would be a difference if there was a degree of assessing efficacy rather than just looking at tolerability. It was noted that efficacy was not usually being assessed as part of a Phase I clinical trial. The issue is that you only know if there is efficacy if it is looked for and if this is set out in the study protocol. JM suggested that it	

	would be biomarkers which were being assessed rather than efficacy. It was suggested that participants take part in clinical trials for a number of reasons such as money and the hope that the treatment being developed may come to the market in the future and help them or others with the same condition, even if it did not provide immediate therapeutic benefit. It was suggested that one way to distinguish patients in Phase I clinical trials was to look at how they were recruited. Was this through their doctor or clinical team or was this through an advert. It was noted that Phase I oncology trials would usually be recruited through the clinical team rather than by advert. There are also some chronic conditions for which the patient may be recruited through either route. It was suggested that this would therefore not distinguish between patient and non patient participants. Further discussion took place regarding equality of payment for time and inconvenience. JK stated that there are a number of other clinical trials which involve the same time and inconvenience as some Phase I clinical trials but the participants don't get paid. It was noted that this was the main issue. JK suggested that if this is the case then this falls outside the remit of this group as this does not relate to participants in Phase I clinical trials. This therefore means that there are many RECs who would experience the same issue but are not part of this particular group. Agreement was reached that where there is chronic stable disease, they should be treated as 'patient volunteers' and should therefore be afforded the same right to payment as healthy volunteers. JM explained that when reviewing the Phase I Accreditation Scheme, this discussion is helpful as they are looking to bring Phase I patient clinical trials into the scheme. It was suggested that as well as patients with chronic latent disease being classed as a patient volunteer, this should also apply to patients who have active disease where there is no potential for clinical benefit. Studies considered by the MHRA as Phase 1 studies must go to a Type 1 REC. First time in-human studies involving patients, usually cancer trials and classified as a CTIMP should to go a Type III REC which is flagged for first-time in patients. However if there was any uncertainty a dual flagged Type 1/III REC would be the safest option.	
4.3	The issue of participants declaring payment from clinical trials for tax reasons was raised and in particular, whether there should be a requirement for this to be stated on the PIS. It was reported that the HMRC website has a section regarding payment from clinical trials. This guidance states that as long as the payments can be deemed to be reasonable expenses then they do not need to be declared for tax reasons. This was considered to be under £8,000. It was suggested that the responsibility should in fact lie with the participant as	

	every person is responsible for their own declarations. CC added that this issue had been discussed by the NREAP in the context of whether there should be a mandatory statement in the PIS and their view was that the PIS contained a lot of information and they didn't want to add more without good justification. It was therefore agreed that there should not be a mandatory statement. It was agreed that the statement would not be mandatory but there was still a preference from RECs that this was included. There was a suggestion that the information provided by the HMRC should be added to a FAQ list. It was noted that the advice was not however the same for benefits as the same rules don't apply.	
5.	**Generic Screening** JM explained that some units quite regularly do generic screening which is undertaken prior to studies commencing so that when there are short timelines, potential participants can be screened with generic information. This is prior to being enrolled into a study and therefore the requirement for ethical approval falls outside current guidelines. JM further explained that generic screening documentation is often reviewed by a REC but this is on a voluntary basis and there is a further added issue when amendments are made to the generic screening protocol and documentation as this falls outside the requirement to submit a substantial amendment. The changes could however potentially be substantial. JM queried whether there should be an expectation that review is undertaken and a notice of substantial amendment submitted when making substantial amendments. An example of this would be when more blood tests are required, who would then be responsible for ensuring that this is approved? It was noted that review by a REC was good practice but not currently mandatory. There was agreement from the REC Chairs present that they would be willing to accept and review generic screening protocols and documentation as well as substantial amendments. JM further explained that generic screening is reviewed as part of the accreditation process and it is not currently clear how the MHRA manage and assess this when there has been generic screening. The MHRA currently make a recommendation but this is all. JM suggested that if ethical review was being undertaken at the discretion of the REC, there would be a particular issue if on inspection the MHRA noted that there had been a request for ethical review to the REC but this had been refused. It was queried whether this involved approval of a healthy volunteer database which hold the details of people who have agreed that they would like to be considered to take part in a clinical trial in the future. It was agreed that this was different as there would not be the same degree of pre screening before being added to the database. JK suggested whether, as with advert review, pre trial screening should also be mandatory and that any changes which fit the criteria for a substantial amendment should also be reviewed. This gives something to reference when undertaking	

	inspection. Discussion took place regarding whether ethical review should be undertaken by individual RECs or through the single Committee who currently review generic advertisements. It was agreed that the review should be undertaken by the generic review Committee. A more detailed review policy should be written to include this. KO feedback that the process was currently working well. It was noted generally that this process was a vast improvement and had been very much welcomed.	**CBl**
6.	**Update on the Clinical Trials Regulations** CC explained that the current EU Clinical Trials Directive is under consideration to become a regulation, which if it comes in will mean that it must be implemented as stated by all member states without variation. In recent years we have seen a decline in clinical trial activity in the EU. The number of clinical trials conducted in the European Union fell by 25% between 2007 and 2011. In the UK, the number of trials fell by 22% over the same period. Although this decline cannot be attributed solely to the Directive, it did have an effect on the cost and feasibility of conducting clinical trials. The expectation is that this will remove the current degree of variation amongst member states and make it more level and fair. CC explained that the HRA & MHRA are jointly leading on the UK response to the proposals. There was no mention of ethics committees in the original draft. New amendments do however refer to ECs and also define ECs. The expectation is that the final draft will mention ECs and this has been raised by a number of member states. In terms of Phase I, some issues where amendments being proposed - - In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based on clinical trials recorded in a publicly and easily accessible database without imposing any cost on the access to the database. Clinical trial data based on clinical trials conducted before the date of application of this Regulation should be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation. Phase I trials are currently not on the register. The proposed regulation states that those participating in research must represents the population to be treated. This may be an issue with healthy volunteers. The MHRA are trying to tweak and influence the language. CC explained that the intention is to implement The Regulation in 2016 but realistically it may be later. RT noted that there was currently concern that progress would slow down during the current presidency. This was currently Lithuania and it was understood that they had less experience of providing this level of scrutiny. The Irish presidency had achieved a full read through but little more than this. It was also noted that there will be a European election next year which may also affect progress.	
7.	**Phase 1 participant populations** CC presented a paper which he had written in response to comments made by Ben	

	Goldacre in his book, Bad Pharma, that homeless people were being recruited into clinical trials. He stated that the paper was not a scientific analysis of data but does give a rough idea of the types of people who participate in clinical trials. It was noted that the majority are employed, either full or part time. There was also a reasonably high number of students and unemployed. It was suggested that there was no evidence that homeless people were being recruited to take part in clinical trials and there were procedures in place that would make this difficult. HR asked whether absolute numbers or percentages had been submitted by the CROs as if just percentages were being looked at, all CROs would have to enrol a similar number of participants to be able to make a comparison. HR also noted that there was one CRO outlier whose data differed from the other CROs. RT suggested that the paper did however address the key issue of whether homeless people were being recruited into clinical trials, adding that there was no evidence to indicate that this was the case.	
8.	**Prefect SSS System** KB from Richmond Pharmocology made a presentation to the group on the Prefect Search Spider System which allows pan European searching of data relating to participants on clinical trials, which have been uploaded to a 'shop window'. **Questions** **What is the cost to the user?** There would be no direct cost to the user for using the system. They would however require a dedicated computer at the site, which is where the information would be held in the 'shop window'. There may be a requirement for further development costs but they would be shared amongst all users however, the expectation is that this would be minimal. **Is there a limit to the number of searches which can be undertaken?** The system is set to a limited number of searches, the limit that is set however can be determined by the user. The view of the working group is that 50 searches a day would be the maximum required as currently users undertake 20-30 per day. Limiting the number of searches to 50 per day will prevent trawling. **Is it fool-proof? What if volunteer insisted that they are not involved in other trials when the system indicates that they are?** Nothing is fool-proof but the CRO should be able to obtain photo evidence and evidence of the town in which the person was born. They can also contact the unit where they are showing as a red flag to verify the information. **Are there any controls on who can access the search function?** Each user has their own log in so that there is an audit trail. The search limit is per unit rather than per person. KB explained that the unit would need to upload the data to the 'shop window' and it is this data which is searchable and not data which sits in the unit's database. The data on the 'shop window' will sit there for a defined period of time after which it will fall out of the 'shop window'.	

	TOPS is the mandated system for the UK, could the TOPS system be updated to interact with this system so that it can undertake pan European searches? The expectation is that TOPS can be updated but it is unclear to what extent pan European searcher could be undertaken via that route. It was suggested that there is no evidence on TOPS that participants travel to the UK to take part in clinical trials. Moreover there are simple checks which can be undertaken to see if someone is not from the UK. KB explained that to date, the Belgians have taken the lead. Chairing of the group will be moving from Keith, although Richmond Pharmacology will retain the IP. The group will be run by another member which will be confirmed on 4 August 2013. This will be someone who is actively involved in issues of over volunteering. JK explained that this presentation had previously been delivered to the MHRA and it was decided that it would be beneficial for the presentation to also be delivered to TOPS users. With regards to how this system would link with TOPS, a technical expert would be required to look into this. **How will different databases link as the information being searched for each database is different?** It should be the same information which is being collected. There may however need to be some tweaking to ensure consistency between systems. **All databases may contain the same information but may be formatted very differently, could it search consistently based on this and in particular as place of birth is not generally recorded?** This system does not search other databases directly, it just searches the 'shop window'. The data is extracted from the database and uploaded to the 'shop window'. This is the only information which is seen. **Therefore does this mean that everyone would have to buy in and maintain their shop window to make the system robust?** The 'shop window' can be a server or computer which remains on 24 hours a day so that it can be accessed at all times. The main risk would be that the 'shop window' is turned off in error. It is therefore suggested that the computer or server is kept in a locked server room. **Does the system need all of the criteria to trigger an alert?** Yes. **Is there therefore a risk of not getting an exact match due to a typing error?** There is software to upload the data to the 'shop window' so that there is no data entry except for initial entry. The system does have built in alerts should the information being inputted not appear to be correct. Such as a date of birth starting with 38 or a place name which is spelt incorrectly, such as 'Leeeds'. **How long would it take to get all the information in such a format that this could be used robustly?** It took 2 people 2 weeks to go back through 90 days worth of data to format correctly. It was suggested that there was a need to gauge acceptability of the group. From an MHRA perspective, they would be happy with this system as long as they have assurance that it is robust.	

	KB asked whether the RECs saw this as a benefit to volunteers? It was noted that it took 10 years to get buy in from all units to use TOPS and still didn't manage to get Richmond to join. RT suggested that regarding the position of the Advisory Group, further consideration would be required at this stage. It was however noted that it was clearly important to monitor on a pan European basis. RT thanked KB for the presentation. JK suggested that the group should provide their views and comments via catherineblewett@nhs.net. From a technical position, the HRA IT expert has concerns with the TOPS platform and thinks that this could be updated. The HRA does however need to be mindful of any cost implications as the initial understanding when taking over the system was that it would not be expensive to run or update. RT suggested that TOPS should be added to the next agenda for this group.	**CBl**
9.	**Allocation and distribution of Phase 1 studies**	
9.1	IS explained that the Hatfield REC has expressed concern that they have recently been receiving very few Phase I studies to review. The major concern is that their expertise will also be lost. The REC would like to understand how it has got to this point and whether there is anything which can be done about it. JK suggested that this should be linked to agenda item 13 as she had Management Information which sets out the number of Phase I applications which have been allocated to each REC over the last 12 months. This information will be circulated to the group post meeting. UKECA have requested information on workload and will be interested to know how expertise is being retained. JK said that the preference is to allow greater choice to companies and therefore there would be reluctance to reduce the number of RECs flagged to review Phase I studies. It was noted that Hatfield Welwyn did unfortunately disappear off the booking system for a period of time which will have had an effect. This problem has now been resolved. It was noted that some of the variation may be due to preference as they have received a particularly good service from one REC or a particularly negative experience from another REC and they are therefore choosing not to submit to that REC. JK said that she had not received any direct feedback to this effect.	**CBl**
9.2	MB said that concern had been raised as there had been a trial booked through CAS which was allocated to a REC which had not received a Phase I study for 2 years and the study was subsequently transferred. The sponsor was not happy that this had happened. MB asked whether there are any defined rules for Phase I in terms of maintaining experience. JK responded that for CTIMPs it is 12 applications per year but there is no such number for Phase I clinical trials. RT suggested that not reviewing a Phase I applications for 2 years would be worrying and that there needs to be the balance of adequate cover in terms of number of RECs against adequate experience.	

	JK said that CBl will be undertaking a piece of work to look at all REC flagging. She would also expect Chairs who are concerned to approach NRES and say that they do not feel that they now have the necessary expertise. It was agreed that Management Information relating to the number of studies reviewed per REC should be brought to future meetings.	**CBl**
10.	**Review of SSA in Phase I Studies** CBl explained that clarification had been requested regarding the process for SSA review by the main REC for Phase I studies in terms of whether this is the process for patients studies. It was acknowledged that the current advice had been that this related to clinical trials involving healthy volunteers only as clinical trials involving patients were not covered by the Phase I accreditation scheme. The distinction should however be between therapeutic and non therapeutic clinical trials rather than healthy volunteer and patients as this was more in line with the MHRA Phase I accreditation scheme guidance. JK suggested that going forward, the hope is that the SSA for all Phase I clinical trials will be undertaken by the main REC but currently Scotland are currently not on board with this.	
11.	**TOPS metrics** RT suggested that if anyone has any suggestion or comments regarding TOPS metrics, they should send direct to JK outside of the meeting. This was agreed by those present. RT suggested that the journal article should be published in the BMJ, maybe as a letter. MB responded that when the paper had been submitted to the British Journal of Clinical Pharmacology it had not been accepted. The other suggestion put forward was to submit the paper as a sponsor editorial. MB suggested that such an article comes from TOPs users or even the HRA.	
12.	**Publishing of Phase 1 Advisory Group Meeting Minutes** All present agreed that the minutes of the meeting should be published in the public domain once formally agreed.	
13.	**Phase I Management Information Data** KB said that as the timelines for substantial amendments were not as clearly defined as the timelines for the review of a new application, this made it more difficult to manage. It was noted that there is a target for the processing of substantial amendments of 35 days, as set out in the Clinical Trials Regulations. KB suggested that this was too long. JS asked whether it would be possible for Notice of Substantial Amendments to be submitted to the REC immediately on receipt. It was noted that this would not be possible as it was necessary for the co-ordinator to undertake a process of validation to ensure that the NOSA is valid and can be reviewed by the REC. If there is a delay in this process then that is an administrative issue which would need to be addressed operationally. Validation should take place within a maximum of 5 days. It was suggested that data on valid / invalid applications should be reviewed at the next meeting. It was suggested that there should be a shortened timeframe for the review of substantial amendments. The average number of days to review in the management information was referred to and it was noted that the average is considerably lower than 35 days. JK explained that for most RECs the average number of days to review would in reality be lower than the data suggested as there was one particular REC whose timelines are outliers and thus increase the average. This has however now improved. JK said that it is acknowledged that some substantial amendments do need to be reviewed	**CBl**

	sooner rather than later. This cannot however just be because of convenience, there does needs to be good justification for this. KB - said that if they had a better defined timeframe this would help as somewhere between 1 - 35 days makes it difficult. It makes it difficult to plan with staff and volunteers when there is so much uncertainty. JK explained that insisting on a reduced timeframe is difficult due to the voluntary nature of the work undertaken by REC members. JS suggested that 15 days should be a reasonable aim. HR said that her REC receives a high number of substantial amendments and reiterated that this does have a significant impact. It was noted that the MHRA are able to turn around substantial amendments within 14 days. It was further noted that they receive payment to undertake this while REC members do this voluntarily. SE said that the length of time which it takes to review a substantial amendment is more often due to the difficulty of reading the NOSA. It needs to set out clearly what they intend to do. JK thanked SE for this stating that this is a relevant point and something that RECs have raised concern about previously. JK added that she has liaised with the MHRA who have confirmed that they will now send back a NOSA if it is not clear what is being asked. It was suggested that RECs also return NOSA which are not clear. RT - suggested that the average from management information should be taken as the expectation. JK said that internally the issue will be looked into and a reminder sent to all staff that Phase I substantial amendments as well as new applications should be prioritised.	**CBl**
14.	**Any other business** MB raised an issue which had previously been highlighted through the TOPS and he would like further clarification regarding how the matter should be dealt with. A person who had previously taken part in a Phase I clinical trial had not received any payment for their participation. It was unclear how this matter should be dealt with. It was queried which would be the most appropriate body to deal with the matter and whether the REC should be informed. It was noted that the REC and the HRA do not have the authority to deal with such a matter but when approached independently they will try to assist the complainant and facilitate the process to try to get a resolution. JM suggested that this may fall within the remit of the MHRA as the CRO has not complied with the informed consent approved by the REC. This would be particularly important if there had been numerous occasions when this happened with the same CRO as this may be reviewed as part of the inspection process. It was not however clear whether anything could be done legislative wise.	
15.	**Date of Next meeting - 6 February 2014** **Increase the time of the meeting - 3 hours.**	