Phase I Advisory Group
Minutes
17 July 2014
11:00 - 14:00

Present

Richard Tiner	Chair	RT
Catherine Blewett	Health Research Authority	CBl
Joan Kirkbride	Health Research Authority	JK
Sue Bourne	Health Research Authority	SB
Charlotte Allen	Health Research Authority	ChA
Deidre McCollam	Biokinetic	DM
Gary Johnstone	BioKinetic	GJ
Malcolm Boyce	HMR	MB
Kath Osborne	GM Central (REC Manager)	KO
Sarah Dobbin	Quotient Clinical	SD
Morag Leaver	Quotient Clinical	ML
Mark Egerton	Quotient Clinical	ME
Christiane Abouzeid	BIA	CA
Keith Berelowitz	Richmond Pharmacology	KB
Ashley Totenhofer	Bloomsbury REC (REC Manager)	AT
Noel Landsman	Quintiles	NL
Anita Chhabra	Cambridge Central	AC
Peter Dewland	AHPPI	PD
Stephanie Ellis	Hampstead REC	SE
Jennifer Martin	MHRA	JM
John Sheriden	Berkshire B REC	JS
Alan Reuben	Westminster REC	AR

Item	Item details
1.	**Apologies** Art Tucker - London City & East REC David Carpenter - Berkshire REC Peter Heasman - York REC Roger Rawbone - GM Central REC Adrian Baillie - Surrey REC Joe Brierley - Bloomsbury REC Jan Downer - Harrow REC Susan Tonks - Berkshire REC Ulrike Lorch - Richmond Pharmacology John Keen - Brent REC Ian Skidmore - Hatfield REC Raj Bains - Oxford A REC Clive Collett - HRA **C Brearly - ABPI Experimental Medicines Group**
2.	**Minutes of previous meeting on:** 6 February 2014

	The minutes were agreed as an accurate record with an amendment to the following sentence on page 5 "Concern had been expressed by *ABPI/AHPPI* members that it is difficult to see how the new process is as efficient as the current service." It was agreed that the minutes of the previous meeting would be published on the HRA website. Any requests for information to be redacted should be sent to Catherine Blewett within two weeks.
3.	**Matters Arising** **3.1 Terms of Reference (to Follow)** CB apologised that this document had not been circulated for comment after the last meeting and agreed to send out after this meeting. **Action: Catherine to circulate the ToR with the minutes for comment.** **3.2 Item 7 on the minutes from 6.2.14** It was noted that CC had agreed to feedback to the group regarding advertising for clinical trial volunteers on job websites. As CC was not present, this was deferred to the next meeting. **Action: Catherine to contact Clive to highlight this has been deferred to the next meeting.**
4.	**Update on the Clinical Trials Regulations** SB gave a brief update in regard to the EU Clinical Trial Regulations . It was finalised, approved and published in the European Journal on 27 May. Work was now focused on working towards implementation. Implementation of the Regulation requires an EU portal and database, the responsibility for which sits with the EMA in collaboration with members. There is a clause that implementation depends on the portal and database being ready in a format that is useable. There will be a 6 month notice published in the European Journal prior to the Regulation coming into effect. It was queried whether the Regulation was likely to come into effect in 2 years as previously stated. It was explained that the MHRA were taking a large role to validate and put the portal in place. Martyn Ward and other GCP inspectors have been working to ensure the portal and database are fit for purpose. The EMA have started working with member states. Several sub groups have been working on areas which feed into this overall work and there has been discussion regarding the content of the database and the specification. It was noted that there needs to be smooth communication. The EMA have been working with stakeholders. With regards to timelines for implementation, it was explained that they should be reasonable but are unlikely to be exactly two years as the work is already six months behind. Some of the smaller member states that don't have electronic systems already will need to set systems up and they will need to be compatible. There could therefore be further delay. RT queried whether there would be a situation whereby some member states started before others and it was confirmed that this would not be the case. JM explained that there have been issues regarding GMP IMP guidance. The GCP inspector working group have been working to ensure that clear guidance is available.

SB invited the group to ask questions.
It was queried what would happen with trials requiring an ARSAC certificate. SB said that she was not aware but that this may be picked up with the ongoing work around HRA Approval.
RT asked those present to go through the EU Regulation to identify areas of concern to highlight at this stage and forward to CB. It was noted that it was not possible to change the Regulation but the group can start to see if issues can be addressed.

Action: All to identify any areas of concern with the EU Clinical Trials Regulation and forward to Catherine.

4.1 Timelines

PD said that he was now reassured that work was being undertaken 'behind the scenes', adding that it was important to represent CRO and Pharmaceutical company interests. There had been concern that they would be disadvantaged by the Regulation in terms of timeframes and concerns about the technology. PD added that members (AHPPI) were of the opinion that, to some extent, it was already disadvantaging the UK. PD said that members would like a promise that the UK will process applications as fast as possible. The timeframe for reviewing substantial amendments was queried and it was noted that currently they were being reviewed quicker than the required time. It was also queried whether, if the applicant has not not heard from REC within 60 days, then can the research proceed, as this does not appear to be ethical. It was suggested that the MHRA have said that they will turn UK only Phase 1 studies around as quickly as they do currently and assurance was sought from the HRA that they will do the same; as there was concern that work from the UK will be lost. JK responded to say that the HRA will ensure that ethical review of Phase 1 studies will be undertaken as quickly as they are currently.

4.2 Allocation of applications to RECs

MB explained that most Phase 1 units use certain RECs to submit applications as they then get used to working with them and this eases the process and queried whether it would continue to be possible to submit to chosen RECs under the new Regulations. JK responded that it was quite possible that to meet the required timelines, submitting to a chosen REC may not be an option under the new regulations.

JK explained that there have been very early discussions regarding how the ethical review under the new Regulation may be undertaken. She expressed apologies to REC Chairs present who had not previously been made aware of these discussions and explained that this was due to some joint Chair/NREAP meeting having taken place before the early discussions had taken place.

JK explained that part 1 of the Regulation has one section which has an ethical element and part 2 has sections which have an ethical element as well as sections which are currently undertaken as a R&D function and will comes under HRA approval process going forward. NRES and UK operational colleagues do not feel it is possible to separate the ethical elements in part 1 and part 2 and the expectation is therefore that they will be considered at the same time. There will be a need for UK legislation to replace the UKCTRswhen the Regulation comes into force and also policy changes, such as what constitutes an ethics committee. The proposed plan would be for the Ethics Committee to review the ethical elements of part 1 in collaboration with the MHRA and for the Ethics Committee to review the ethical elements of part 2 independently with the non ethical elements being undertaken by administrative staff within the HRA. Currently an Ethics Committee has a quorum of 7 but to meet the requirements of the Regulation this may be 3 or 5, as the

	current system would not cope with the requirements of the Regulation, in particular the timeframes. Early thoughts included having a pool of experienced Committee members and when applications come in, members will be taken from the pool to work with the MHRA and undertake ethical review. JK made reference to an article in the British Medical Journal which had suggested that the Regulation would weaken the ethical review by including and ethical element in Part I. It was noted that the intention in the UK however would be that this is not the case as UK policy will require research ethics committee members to be involved in the review. JK added that the proposals from early discussion had been well received by REC Chairs so far. There may be a requirement for a REC to meet every day of the week to meet the demand. Consideration could also be given to charging for this service but it was unclear at that time whether this would happen. It was queried whether meetings would be face to face or held virtually as having such regular meeting face to face could be problematic. JK responded that the expectation would be that the meetings are virtual but another option would be for the REC members to meet face to face with the MHRA representative attending by teleconference for the relevant section only. It was early days and there was time for more thought around proposals. JS commented that it would be unfortunate if it was not possible to select the REC to which an application is submitted as it does work well when RECS and CROs develop a good working relationship. It was suggested that improving consistency between RECs would improve the overall situation. KB suggested that sponsors would probably accept paying if they could guarantee fixed timeframes, adding that Ethics Committees could potentially convene daily if was 'professional' ethical review. JK explained that this meeting is specifically considering Phase 1 research but the Regulation applies to all CTIMPs which is a considerably greater number overall and this would need to be given consideration. JS queried whether it would be considered unethical to pay for ethical review. JK explained that previously some members would support payment however the majority view was that the volunteer approach was preferable. AC queried what would happen in regard to attendance at the meeting. It was noted that this would have to be something that was given due consideration as sponsor/investigator attendance at the REC meeting was seen as a very important element of the process. JK explained that another new initiative the HRA is taking forward is a process where someone contacts the applicant in advance of the meeting to discuss things which are not clear and also to prepare them for the meeting. This may involve suggested changes to the supporting documentation which could mean the study receives a favourable ethical opinion rather than a provisional opinion. This would continue under the new Regulation as this administrative non ethical element would be picked up by HRA staff. SE explained that she had been involved in the initial pilot for this process and that the process benefited in two main areas, helping students with the overall process of ethical review and also for clinical trials as it ensured that the applicant was better prepared and had what they required on the day of the meeting. ME queried what the timeline for review and approval or Phase 1 research is expected to be under the Regulation to which JK responded that the discussions were not this far along at that time. ME added that Quotient Clinical had previously worked with US Pharmaceutical companies who had vetoed the UK as timelines appeared to be too long, on paper. They had tried to explain that in reality this was not the case and the timeframes were in fact much

shorter but it took considerable work to build this confidence and to bring the work back to the UK. There was concern that if the timeframes become longer, even if this is just on paper, the confidence will be lost and therefore the work will be lost from the UK. It was noted that the EU Directive had longer timeframes on paper but in reality approvals were given in much shorter timeframes so the situation will not be different. RT suggested that there should be work undertaken to get the message out that the UK do have competitive timeframes to review and approve Phase 1 research by placing articles in relevant publications. It was noted that discussions had already taken place with the Head of Communications regarding this. ME added that current timelines are very good and competitive which puts UK companies in a good position to get this work.

KB explained that he had sent out a survey to sponsors and intended to present the results at an upcoming HRA training event, adding that he would welcome putting out some articles which made clear to sponsors how quick UK timelines are for review and approval of Phase 1 research. Sponsors need to know what's going on in simple terms. KB added that there also has to be consistency between RECs. CROs chose RECs as they know that they will give a decision within a certain timeframe.

ME explained that what is important to Sponsors is 1st Subject 1st dose and therefore to plan all required approvals to co-ordinate the 1st subject 1st dose. ME suggested that it would be worth talking to CROs to ensure that policies which are agreed allow for this process so that 1st subject and 1st dose happens on the planned day. JK stated that everyone was on the same side in this regard and that it was the aim of the HRA to promote the UK as a place to undertake research, adding that the HRA will do what it can to make the UK competitive.

KB suggested that the public relations work needs to start immediately. If sponsors see information in print then this will give them some reassurance. It was agreed that it would be important to get the communications right and that this should not wait until implementation.

It was agreed to add information to the HRA website which included communications to give reassurances. JK suggested that as part of the annual reporting process some key facts could be published. The MI data for the last year could be published and this could be made into a good news story. It was also suggested that an article could be developed about the Advanced Phase 1 training course which had been developed and was being rolled out soon. There was suggestion that a symposium could be arranged with the aim of promoting the UK as a lead in clinical trial research as this would most likely get a strong attendance.

Action: Catherine and Charlotte to set up Phase 1 area on the website.

4.3 Process for completing and authorising application forms - investigator involvement.

SB explained that a single application will cover what is currently the Competent Authority application and the Ethics application. This will be regardless of the number of member states within which the research is planned to take place. The content for the application is under development. SB added that work had started in regard to the users of the portal from the applicant perspective and that consideration needed to be given to the fact that it will not necessarily be one person completing the whole form. There is a good amount of time allocated for portal testing which will include testing of the applicant user interface.

	NL queried whether if there was a multi site study in the UK and the lead site submits the application, would other sites still require a separate SSA. SB responded that it is a single application process and the application will describe the sites but it was unclear what would happen if the sites were unknown at the point of application. Some elements will be picked up by administration role. The intention is that there will not be any duplication. RT queried whether there will be a transitional phase. JK suggested that in the first instance, the process will be tested for acceptability with the MHRA and REC Chairs and then take it from there. Live testing would not be realistic as there would need to be legislative cover for any ethics review. It was queried what the timeframes for substantial amendments would be under the Regulation. It was noted that amendments would be referred to as modifications under the new Regulation. Further work needed to be undertaken in this area. It was agreed that the EU Clinical Trials Regulations would remain as an agenda item with his priority. **Action: Catherine to ensure that EU Clinical Trials Regulations remains on the agenda.**
5.	**<u>Transparency in Phase 1 research</u>** **5.1 Please provide any examples of sponsors raising concerns regarding the transparency requirements within the UK; for discussion.** No examples received for discussion MB explained that this matter had been addressed at a separate meeting and that he had fedback through this other forum. It was suggested that there was general unrest in phase 1 units that registration and publication would lose business to the UK. ME stated that he was aware that the European Medicines Agency (EMA) had recently pulled back from publishing their transparency agenda with the expectation that this will be published in October. This was due to conflicting information. It was noted that the European position is yet to be defined. What is clear is the commercially confidential information will be recognised but there has been no definition of what CCI actually is. Work is ongoing but this needs to be clarified. It was noted that since the option to defer registration was brought in, there had been a 50/50 split regarding which sponsors chose to take this option. Sponsors in the US usually defer, particularly for very early stage research and this is due to concerns around commercial sensitivity. It was suggested that those sponsors who don't request to defer registration, may be at phase 2 already. It was also noted that GSK have a transparency policy. KB stated that the results of the survey which Richmond Pharmacology had undertaken indicated that the majority of responders said that they were not happy with making information regarding early phase trials public. RT suggested that there had previously been concern that companies were hiding behind 'commercial sensitivity' when this was not actually always relevant. Studies which are closer to 1st in man are more likely to be relevant. ME suggested that the starting point should be that transparency is important but to also acknowledge that there is a risk if the UK move ahead of others. 60% of industry is US

	based. The way forward should therefore be to harmonise with the FDA and work with regulators to develop a transparency policy. It was further noted that Sponsors do accept registration at Phase 2 of research. It was noted that companies which are smaller and still developing which have invested in novel targets and mechanisms are concerned about larger companies knowing what they are doing. Other companies are also developing molecules which could be a best in class product. They need to work on this to make it best in class so if made public then this lets competitors know that there is a weakness. This would have an effect on starting up new companies in the UK also as they may choose to send the work out of the UK to avoid having to make their research public at an early stage. JK stated that Janet Wisely had provided some feedback to share at the meeting. - The HRA do not think that registration presents issues regarding commercially sensitive information, but do accept that others have concerns in this regard and that is why there is a simple mechanism to defer registration as long as there is a commitment to register at a later stage. - Registration is vital so that there is evidence that research has been conducted, whether that be for patients, public or other researchers. The HRA accepts that the patient interest in healthy volunteer studies is less than research involving patients but there are still issues regarding safety and repeating studies etc. If studies are registered they can be identified and the results sought. - The Clinical Trial Regulations will require registration of early phase research. The HRA believe that the UK will be at an advantage over the rest of the EU if they address registration at this stage rather than waiting for the Regulation to be implemented. - The feedback received to date has been mixed. The main issues have been around UK competitiveness and commercial sensitivity. - The HRA are looking to set standards for putting findings of research in the public domain. There have been initial discussions at a HRA workshop and this will be followed up in September 2014. The HRA noted at the workshop there may be a case to be made for timing of making findings public to be longer for phase 1 and the HRA sympathetic to that. - The HRA is mindful of the issues with data and Industry concerns about commercial sensitivity, plus wider issues around resources to provide data, the value of that data provision in all cases and also issues of potential confidentiality issues if patient level data is provided. The HRA signed up to AllTrials but have welcomed the more pragmatic approach that has emerged about trial data. The HRA think the GSK approach, which involved a panel review to grant access, has merit. HRA is part of the debate and welcome the continued debate in what it recognises are complex issues, the practicalities and complexities should not be excuses to avoid transparency but they may present good reasons for stepping back and thinking about the most effective approach when it comes to trial data. Link to the transparency consultation page on the HRA website. http://www.hra.nhs.uk/about-the-hra/consultations-calls/registration-and-reporting/ MB requested to ensure that due consideration was given to companies who are working on novel developments and therefore do not want competitors to know. MB added that it is accepted that some information will be in the public domain, such as the PIS and if a competitor really wanted to find out they could but the preference was to not make the information easily available. There was concern about the situation should deferral of registration no longer be an option. JK confirmed that deferral will remain in place until the EU Regulations state otherwise.

	CA explained that the meeting of the EMA in October will be in regard to the information submitted in the application and not the commercial sensitivity of the information available through registration of the study. CA queried whether CRO representatives were against the principle of registration in general or just the UK being first to take this step. ME responded that he did not understand why the UK would rush ahead if it makes the UK less competitive as sponsors would just go to other countries where they don't have to disclose. CA noted that the information which is made available through registration is not a lot of information. It was suggested that even a small amount of information was enough to let competitors know that there is something to investigate further and this will therefore make it easier for competitors. RT suggested that there was an issue with non registration in that if a previous trial was quoted in a new application, if this trial was not registered then this would not be accepted as a trial. Retrospective registration would therefore be required. The EU and also the Sunshine Act in the US will ask for this. It was suggested that something from the ICH would be required on this matter. There is an international issue which needed to be worked through so that the US, Japan and EU work together. JM stated that the ICH have looked at GCP E6 so this maybe something they could look into. RT suggested that the area needed to be addressed is attrition. It should certainly be the case that where a drug does not proceed further then this research should be registered. It was agreed that this should be the case for reasons of safety. ME suggested that there was a danger that with the EU Regulations, there would be no confidence in timelines and sponsors may decide to take work away from the EU for a period of time and and see how it works out before giving consideration to bringing work back. There needed to be international harmonisation. **5.2 Publication of the summary of opinion for Phase 1 research.** JK provided an update regarding the publication of the summary of opinion on the HRA website. Work has been undertaken to transfer this function from the NRES website to the HRA website. The expectation was that all research summaries would be uploaded to the HRA website 3 months after the final ethical opinion is given from summer 2014. JK added that there was an option to defer publication of the research summary and that the same process for requesting deferral of registration should be followed. JK explained that there were similar issues for the medical device community as had been raised by the Phase 1 community in regard to commercial sensitivity. Consideration had been given to whether it was possible to pull some basic information from the PIS to put in the public domain as this information is already in the public domain. It was agreed that transparency should be kept on the agenda for the foreseeable future. **Action: Catherine to ensure that Transparency remains on the agenda.**
6.	**<u>Generic Screening documentation</u>** JK explained that a committee had been convened to review generic advertising materials for recruitment to Phase 1 trials and that this had been successfully running for some months now. Requests have often also been received to review generic documentation provided to potential participants at the screening stage. The HRA requested to have a

	discussion regarding what documentation should be reviewed as part of this process to meet the aim of ethical review. It was unclear whether the requirements were CRO specific or something that was wanted more broadly. Requests to date have all been accepted for review but the view was to standardise the process. Review of Phase 1 adverts was mandatory but further consideration needed to be given to documents for generic screening, particularly in terms of the ethical value of a review and ensuring that potential participants are protected. It was agreed that representatives from CROs and representatives from ethics committees would meet to work through this and to develop a list of what should and should not be sent to an ethics committee in regard to generic screening. KB added that it would be helpful to define what is meant by generic screening to ensure that this is always consistent. JM explained that this was an issue which arose during inspection. If the documentation has ethical approval then this is clear but then there is a further issue when changes are made and it is then unclear whether the revised version would be classed as having ethical approval. JM stated that it was of concern that in theory, anything could be undertaken as part of the screening process as this does not require ethical review and approval. It was suggested that there should be some clear guidance regarding what is acceptable, what should be submitted, what doesn't need to and what changes should be submitted for review. NL suggested that as there is no form to complete and it is not a formal route, it would need to made clear how official the process is and what it actually is, i.e is it ethical approval? JK explained that the current process involves e-mailing the documentation to a specific e-mail account. The documents are forwarded to the committee to review and then a response is sent out to the applicant by e-mail It was agreed that consideration would also need to be given to review of generic screening documentation when timeframes are tight and CROs want to undertakeas much screening as possible in advance of the ethical approval so that the first participant can be dosed as soon as possible. There needed to be a definition of when this would be acceptable. **Action: Catherine to find some REC Chairs to be involved in developing this guidance with CRO representatives.** **Action: Keith to arrange for CRO representatives to be involved with this work.**
7.	**<u>TOPS</u>** ChA gave an update regarding the changes which had been made to TOPS and explained that user testing would be undertaken with a view to the system going live in Summer 2014. ChA explained that representatives from CROs had agreed to assist with the user testing but asked any other representative if they would like to undertake testing to contact her. ChA stated that with the new database, there is an alert tab which alerts to records which have not been updated which meant that is was important to ensure that records are updated regularly to avoid numerous alerts. KB queried whether data would be retained for those who were not dosed. ChA explained that as soon as 'never dosed' was selected, this data would then not be viewable to any CRO except the one which created the record. If the record is not updated, the record will

	continue to be viewable by other CROs. JK raised an issue which had been brought to her attention. ICON had closed their clinical site but have kept one phone available to call and have kept the database open so that they can answer any queries required via TOPS. They were not however sure how long they would need to continue to do this and to retain the information. JM suggested that this was not so much about TOPS, unless they have contact details in the master site file. It was more relevant to how they could contact the participants in case of additional safety information regarding the trial they took part in. For most CROs most of the contact details are included in a database and not screening files. **Outcome - suggest that ICON contact the MHRA to clarify how long they need to keep the information.** **Frequently Asked Questions document** JM suggested that when using the NI number as proof of identify, evidence should be requested. JM suggested that even when a participant was known to have been given a placebo, they should not be enrolled into a new study if they had more than 100ml blood taken. It was further suggested that being given a placebo should just be classed as dosed. This was because even if the participant had a placebo then most likely they had more that 100ml blood draw. JM requested whether it could be included in Q10. That the MHRA would be informed of any identified non compliance with the use of TOPS as part of the Phase 1 accreditation scheme. NL queried whether there is provision in TOPS to pick up people who are refused for enrolment at one site so try and enrol at another site. CB responded that TOPS isn't designed to identify this level of deviance and it is therefore unlikely that this would be picked up. RT explained that there had previously been discussion around keeping a 'black list' but it was advised that it would not be permissible to keep such a list centrally. It would therefore be for the sites to manage locally. It was queried how it would be possible to know when someone has dual passports. JM suggested that it is sometimes a clue when looking at the place of birth and if non UK, the question could be asked. There is a further issue in regard to renewal of a passport as a new passport number is generated. It was suggested that if a passport is noted to be newly issued, the previous passport number could be requested. It was suggested an existing entry alert would be beneficial.
8.	**<u>REC review of Phase 1 research</u>** MB said that he wanted to discuss this item as there was an apparent inconsistency of ethical review between different RECs. This was even to the degree that one REC could give a favourable ethical opinion and another REC could give an unfavourable opinion. Even simple procedures can cause problems.

	It was noted that this issues was being looked at by the National Research Ethics Advisors' Panel which has produced a document to try to address this issue. The document has been distributed to REC Chairs. It was requested that the consistency document be distributed with the minutes of the meeting. **Action: Catherine to send out the consistency paper.**
9.	**Communication between HRA & Phase 1 research organisations** It was requested that the HRA send out communications in advance of changes being made, possibly in the format of a newsletter. JK stated that when there is a specific change which affects a particular group, information is sent directly to representatives of that group. Information regarding important changes is also included in the HRA e-mail signature. There is also a HRA newsletter called, HRA Latest, this does however need to be signed up to. The link to sign up is the following http://www.hra.nhs.uk/about-the-hra/our-publications/
10.	**Phase I Management Information Data** The Management Information was noted.
11.	**CRO Data** This item was raised and discussed under item 7 - TOPS.
12.	**Any other business** **12.1 Revision of NRES SOPs** CB updated the group that a significant revision of the SOPs had been undertaken which had unfortunately taken considerably longer than had initially been anticipated. The revision was however nearly complete and the revised version would therefore be available in approximately three months.
11.	**Date of Next meeting** **10 February 2015**