Phase I Advisory Group Minutes

30th October 2018

Minutes of previous meeting on 29 March 2018

The minutes of the previous meeting on29/03/18 were confirmed as an accurate record with the exception of section 6 which related to what would happen if the data was being processed in the USA.

NB to amend this and ensure the latest minutes are available on the website.

Matters Arising

The group had previously suggested that it would be helpful if the HRA published the common problems seen in applications in the hope that they could be addressed before submission.

NB confirmed that the 'common issues' presentation delivered at the last P1AG group had been made available on the website. The information had also been fed into 'top tips' slides used by the HRA when presenting externally. The common 'Grounds for Non-Acceptance' from the MHRA and REC were being tracked under the combined ways of working pilot with a view to compiling and jointly publishing the common issues information together when appropriate. A workshop had been planned to further to discuss how the data could be used and embedded into website content, guidance and training.

PD noted an area of inconsistency in relation to RECs accepting the payment amount to be included on trial specific participant facing documentation. PD agreed to send CB the examples of RECs not accepting this so that it could be picked up with the REC's.

TOPS System Change Request

The group referred to item 4. A suggested change to TOPS had been received from a CRO.

Suggestion 1:

Volunteers could be registered on TOPS at any number of sites without restriction. It was suggested that TOPS be amended to only have one open record on TOPS. The proposal was that when a volunteer is registered but had an open record, a message would appear to say 'registration cannot be completed due to an existing TOPS entry'.

The group thought that this would make it difficult for the volunteers who are registered and/or screened at more than one unit. The group suggested that better communication between the units was preferable. It was added that collaboration between the units was working well in London.

It was added that if registration was only allowed at one unit, the potential for participants with dual nationality registering with several passports could increase.

Suggestion 2:

TOPS included the long term follow up date for volunteers who had been dosed. It was suggested that the TOPS record should also include the half-life of the study drug to remove the need to request the information from units.

The group commented that this would not always be feasible because the half-life is often not known until later on in the trial. There was concern that inaccurate information would be added which would disadvantage TOPS users.

Outcome- neither suggestion was agreed by the P1AG.

There was discussion about the removal of the monoclonal antibody box. This had been replaced with 'biological product'. This change had been agreed by the P1AG but several of the group agreed that the original term was more helpful. CA agreed to look at this.

Phase I Management Information data

A phase I MI Summary report had been distributed for 1 Jan 2018- 30 June 2018.

The data included the mean number of calendar days from review to 1st opinion and the mean no. to review split by decision type as requested by the group.

It was noted that the mean time review for Oxford A was skewed by one application which took longer to review because of the requirement to seek expert advice. The mean was not a reflection of how long the REC take to review phase I applications.

The data pulled to generate the report had also highlighted that the withdrawal rates pre-submission were still over 20%, this was sometimes leading to the slots not being utilised, particularly when the withdrawal were close to or on the submission date.

The group thought that the withdrawals might be coming from the smaller units. It was commented that it is often the IMPD information which was not provided in time for submission. This would also explain why there was a higher percentage of withdrawals from the CWOW pilot which is more reliant on submission of IMPD information at the same time.

There had been a couple of incidence of applications being withdrawn post- submission, one of which was after the members had received and started reviewing the application. The group thought these incidence were few and far between but agreed it was something to keep an eye on.

It was noted that the data said that Berkshire had only reviewed one Phase I application which was not correct. NB agreed to check and amend the report accordingly.

General Document Review

The group referred to item 6.0. There had been no great change in terms of the submissions being reviewed by the generic review group. There had been a number of attempts to submit GDPR

wording or privacy notices but these could not be reviewed by the group. Such requests were being sent back with the request to use the standard wording on the HRA website to ensure compliance. Applicants wishing to use different wording were being re-directed so that their wording could be considered and agreed.

There were some cases were the group were giving the same feedback to the same company for every submission. Attempts were being made to identify these submissions before they were sent on to the group to avoid this. The hope was that the feedback from the group would be built back into the development of new materials.

It was commented that the marketing manager working on the documents may not be the person submitting and acting on the group's responses. KB would supply their marketing manager's details in case there were ever any incidence of feedback not being built into new submissions.

It was commented that the group often request use of the term 'clinical trial'. Simbec had received feedback from PPI groups that lay people often associate the term trial with court. The PPI group had also thought 'medicine' was more appropriate than 'drug'.

DR- confirmed that they did think usage of the term 'clinical trial' was important. When the group were more lenient about this it tended to not be clear what was actually being recruited to, particularly for social media adverts with character restrictions. The term 'research' would be acceptable in some circumstances but 'clinical trial' should be used for early stage trials.

JS- commented that it is not always clear in submissions when generic documents have been approved because there is no formal letter issued. It was confirmed that the area on the hub can be referred to, to check that the documents have been considered by the group.

It was noted that non-accredited units sometimes pushed the boundaries of what should be submitted and agreed by the generic review group. JMa wondered if a blog could be produced to better communicate the purpose of the group to the non- accredited units.

MHRA and HRA- Combined Ways of Working Pilot

CB presented a slide set updating on the progress of the combined ways of working pilot. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/

21 applications had been submitted to the live pilot, 6 of which had been phase I. 12 of the applications had completed. The mean turnaround time had been 34 days with a range of 23-47days (with no clock stops).

The information about the pilot had been made more prominent on the HRA website but there would be a requirement to limit the number of applications submitted through CWOW until more of the committees were involved in the live pilot phase.

The preparatory work with RECs was focused on reviewing the new application dossier format which does not include the IRAS form.

CB was chairing an EU group exploring which of the Annex I documents could be templated in a future state to improve consistency.

KB gave an overview of how his committee were finding the early stages of the non-live pilot. One member had reported it taking 8 hours to review one dummy dossier. KB thought guidance about where to find the information without the IRAS form would be key. SE added that her REC, particularly the lay members had initially been uneasy about navigating around the dossier but had settled into the new process.

There had been agreement that the MHRA would complete and supply their Part I Assessment for the live pilot applications. It was hoped that this would give REC members assurance and clarity about the elements of review covered by the MHRA. A workshop with the MHRA assessors, REC Chairs' and pharmacists had been planned to better define the roles within the part I assessment.

DR added that the PIS is key to the RECs review process and thought it would be important for there to be some level of check across the protocol, IB and PIS to ensure the risks were accurately described to potential participants.

JM added that the process changes could be significant for sponsors too. The reduced time to respond to requests for information had been identified as a challenge for the sponsors with multi-layered document sign-off processes.

The group discussed the current allowances made for Phase I applications and asked if the intention was to retain them under the combined process. It was confirmed that the 14 days for the initial review would still be possible for the MHRA but less feasible for REC because the REC meeting dates are not flexible. 7-day submission for phase I applications was not being considered at this stage of the pilot but may be picked up at a later date once committees are used to the new process. The focus was on reducing the time taken post-review. The element of co-ordination between the MHRA and REC at the front-end of the process should reduce the timeframes at the tail end of the process.

JS had submitted applications through the live pilot, the average turnaround for a final opinion had been 32 days which was an improvement overall. One of the benefits had been less need for protocol amendments directly after approval to meet the MHRA's requests.

The current standard operating procedure states that the REC decision letter should be sent within 10 working days from the meeting to allow for the minutes to be written and ratified by the Chair. KB added that this amount of time to turn around a letter was difficult to explain and justify to clients.

JMa- added that New South Wales were in the process of devising a Phase I system, this coupled with their quick timeframes had the potential to attract more companies.

The P1AG agreed that retaining the low timeframes for phase I applications was critical and suggested that the write up and sign-off of phase I applications be done before all other applications. It was agreed to take this forward as an action.

BREXIT

The group were asked to feedback on any questions arising from BREXIT.

Simbec had been asked by American sponsors if clinical trial data would be acceptable to the rest of the EU post-BREXIT.

The MHRA message that it was business as usual for the time being had been helpful. The consultation they had released offered pragmatic solutions to the 'no deal' questions.

MB had not seen any slowdown in the number of trials being submitted to the UK as a result of the 'no-deal' discussions. There had been feedback that many came to the UK because of the advice given by the MHRA. The currency slide against the dollar had the potential to act as an incentive.

DR added that the MHRA were working hard to get a UK representative on the ICH panel.

CB reassured the group that the UK were still very much involved in the CT regulation conferences in Brussels and had been asked to lead on the templates work.

Transparency in Phase 1 Research

At the last P1AG meeting BD had covered the plans to promote transparency in research.

Following the meeting and subsequent conversations with P1AG members, a Project Initiation Document had been taken to the leadership team. It was agreed to exclude Phase I from the project.

The select committee focused on research in universities. Comments around clinical trial transparency were covered in the report released on the day of the P1AG meeting (30.10.18).

Any other business

MHRA Blogs

JMa confirmed the MHRA were working hard on developing further blogs. They would also be considering the dose escalation guidance. JMa agreed to issue the links to P1AG members. MB confirmed that the existing blogs had already been used to demonstrate to sponsors that the MHRA are pragmatic and sensible.

P1AG Chair

Allison Jeynes-Ellis tenure with the HRA was due to finish in December 2018 meaning a new Chair for the P1AG group.

In the first instance members of the P1AG were asked to send declarations of interest to CB catherineblewett@nhs.net