Phase I Advisory Group Minutes

02nd May 2019

Minutes of previous meeting on 29 March 2018 (attachment 2.0)

The minutes of the meeting held on 30 October 2019 were agreed as an accurate record.

Matters Arising

The matters arising were covered within the body of the agenda.

Transparency

CB gave an overview of the transparency briefing paper provided.

The House of Commons Sciences Technology Committee had published a report about research transparency in clinical trials. There was an improvement in the registration of clinical trials but there was still some way to go. The report offered a number of suggestions:

- establish a programme to monitor compliance with requirements around registration and publication of clinical trials
- prepare a funding proposal to the Government to fund such a programme
- publish information gathered through the monitoring programme about the individual trials which have gained ethical approval but a) not registered within the expected timeframe, and b) not published in an academic journal within the expected timeframe
- develop within 12 months a detailed strategy for achieving full clinical trials transparency; and
- introduce a system of sanctions to drive improvements.

The HRA had developed a Research Transparency Steering Group to support the development of a strategy to achieve compliance with the transparency requirements and inspire confidence in research.

The draft version of the public strategy was due to be published in the summer of 2019 for public consultation. A discussion about the outcomes would be held at the next Phase I Advisory Group meeting.

ARSAC Timelines

It had been raised by the group that ARSAC reviews are sometimes taking 3 months. The HRA had met with ARSAC to discuss. ARSAC faced significant challenges recruiting expert volunteers to their expert committees in the same way that the HRA often struggle to maintain clinician membership on REC's. ARSAC were operating on a small budget set up and agreed many years ago and were considering options to secure funds.

ARSAC had asked that they are made aware of specific cases where there are issues directly caused by the ARSAC delays.

The group asked that Phase I was raised in the discussions with ARSAC too because of the short timeframes and resulting impacts. ARSAC predicted a 6-8 week turnaround but it was often taking 12 weeks. Set timeframes were critical for the Phase I community. Not meeting the predicted timeframes had led to significant financial losses such as PET scan cancellation costs, delayed trial start up and resulting product wastage.

It was noted that HRA approval could not be released until ARSAC approval was in place. It was the long- term ambition to be able to tie up the ARSAC communication points with other regulatory approvals but this was not feasible until the resource issues were resolved.

The group agreed that it would be helpful to have a better understanding of the ARSAC process steps and where the delays were occurring. The complex trials, for example, appeared to be taking longer to approve which gave the impression that the committee were reviewing the submissions in good time or perhaps that there was a proportionate review process where the exposure to radiation is below a certain level. The group wondered if the meetings being virtual were supporting or hindering a timely review.

The Phase I Advisory Group discussed the potential ways they could support ARSAC. Overall, there was agreement that the Phase I community would be willing to pay a greater fee if shorter timeframes could be guaranteed. Alternatively, if there was greater awareness of the standards being worked to, commercial companies could be hired to do the analysis of radiation risk pre-submission so that ARSAC could take a proportionate review approach.

The group agreed it would be valuable to have a representative from ARSAC at attendance at the next P1AG so that there could be a discussion about how best to support one another.

Action- NB to discuss with TA and AN and extend invite to relevant representative.

The HRA radiation assurance team had undertaken an analysis of the issues raised by the radiation assessors, the learning from this was being built into the IRAS QSG guidance to support applicants in providing the required information at initial submission stage.

TOPS (attachment 6.0)

The HRA had received enquiries regarding why TOPS was limited to Phase I in research and could not be used for all healthy volunteer research. The group referred to the paper submitted on the proposed expansion of the scope of the TOPS system. It was proposed that the scope was expanded in order that it can be used on a voluntary basis for any interventional research activities with healthy volunteers. It was noted that some of the projects which this could apply to would be reviewed by University Ethics Committees as opposed to and NHS/HSC Research Ethics Committee as opposed to an NHS/HSC Research Ethics Committee and therefore could not be mandated or monitored.

Some members of the group confirmed that TOPS was already used in this way. The non-registration on TOPS created unnecessary work. For example, there were 72 trials in hyper tension ongoing. Recruitment teams could not be expected to call 72 units to find out potential participant information. Sites needed to know this information to accurately assign benefits/side-effects and to

ensure an appropriate washout period was in place. TOPS helps ensure that participant's aren't getting two drugs at the same time, supporting the trial data's integrity.

The group appreciated that the use of TOPS could not be mandated or monitored for academic sponsors by the HRA or MHRA but thought that it's use should be very strongly advised. Encouraging the usage of TOPS was not a big ask but policing it would be a huge effort due to the lack of overarching authority for university ethics committees.

The group thought there would be value in also adding some patient's to TOPS too, particularly if there would be no therapeutic benefit as this type of patient group are often paid and therefore have the same motivation to over-volunteer.

The group went through the questions within the paper:

Would the group be content for the HRA to adopt this approach in terms of the use of TOPS?

-Yes, include the word 'pharmacological'. TOPS should be used for all non-therapeutic, interventional research. If participation is through the treating clinician for example, it would not require entry onto TOPS.

Is there any justification for confining the use of TOPS to Phase 1 research?

-No

Would this proposal present any problems which we have not considered?

-Noted that non- therapeutic vs therapeutic is badly defined.

How would the change be best communicated?

- Using the website and links and meetings with academic sponsors and applicants.

Do we need a check box on TOPS to specify whether the study was Phase 1?

- No

SSI's for Non-NHS Sites

CA gave an overview of the paper provided. As part of the planning for the Combined Ways of Working pilot and in developing the new IRAS, the HRA, in collaboration with the Devolved Administrations, had taken the decision to remove the requirement for the full non-NHS SSI form in IRAS to be submitted and reviewed by the Research Ethics Committee. An assessment will continue to be made in relation to the suitability of the site and Principal Investigator but this would be undertaken in a more proportionate way as part of the assessment process rather than as part of the ethical review process.

It was hoped that this would streamline the process for applicants and reduce the associated review time for volunteer REC members.

Updates to the IRAS guidance were in progress.

Phase I Management Information data

The group referred to the Phase I in Healthy Volunteer MI data provided.
It was suggested that it would be helpful to include a ratio as well as a mean for clarity.

Action- NB to add ratio to future MI reports.

SM noted that there was still a 20% withdrawal rate pre-submission resulting in a concern about slot loss and impact on other customers. There was a desire to keep allowing reservations for Phase I research but this was having a knock on effect on other applicants. The withdrawals were often unavoidable, it was agreed the key was to cancel as far in advance as possible so that other applicants can book to the meeting slot.

There had been an incident of a company reserving slots on two committees with different deadlines as a precaution, but this was thought to be an isolated incident.

Generic Document Review

It was queried and confirmed that generic recruitment activities were within the scope of the group. It was highlighted that the context around the use of the material is key to the GDR committee review.

It was raised that some committees were reviewing and commenting on generically approved documents. It was agreed that it needed to be clear when documents were generically approved and suggested that they are not submitted with individual applications. Committees had the option to request sight of the generically approved documents 'in-house' should they want to review within the context of the trial.

BREXIT

KD raised a concern that straddles both BREXIT and Transparency. The new EU CT regulation would bring about a requirement to submit specific clinical data. If however, the trial was in progress pre-regulation, the sponsor might not be in a position to meet the transparency requirements.

It was agreed that this was best clarified at an EU level as the UK would align to the outcome of the EU discussions.

It was noted that the transparency rules were in the process of being agreed by the EMA. The current exemptions had been carried over into the portal. The criteria for publication would be clear once the regulation was in place but what the requirements in the interim needed clarification.

Action- CB to raise at an EU level.

MHRA and HRA- Combined Ways of Working Pilot

CB provided an overview of the Combined Way of Working pilot.

Action- CB/NB slides to be provided to the group with the minutes.

It was commented that it would be helpful if the data presented included median's as well as means. Capturing and detailing the range in applicant response times would give a more accurate picture of the actual review times.

It was asked if the CWoW applications were being sent exclusively to the RECs with short turnaround times. They were not, but it was acknowledged that the applications being submitted to the pilot were generally very high quality which could be impacting positively on the timeframes.

There was a query relating to where HRA approval came into the pilot. Best efforts were being made to release confirmation of HRA approval with the CTA and REC approval. If, however this was not possible, for example, when there was another regulatory approval outstanding, release of the combined MHRA and REC decision was not being delayed and HRA approval was being sent separately at a later date.

It was commented that it would be helpful to have sight of the applications progress through the process and what was outstanding. It was confirmed that the intention was to have a dashboard system at some point.

The group asked what would happen if the UK did not get access to the portal. It was confirmed that 'New IRAS' would be the front door, beyond which would sit the HRA and MHRA system. The system was being built in a way that was relevant to all access possibilities.

CB confirmed that the HRA's staff restructure had been rolled out on the 1st April. Many staff had been assigned to new roles and it was a difficult time for those settling into their new positions and teams. There had been delay's where there weren't previously. The group were thanked for their patience during this period of transition.

The re-structure was not directly linked to the combined way of working pilot but the findings had been fed in. A support and advice role (Approval Specialist) at REC meetings had been built into the structures so that the REC related job roles were not admin focused and straddled both the REC review process and the HRA assessment. Post- meeting they would have a role in reviewing the minutes and potentially reviewing the responses to provisional opinion. It was hoped that in time this would reduce the time taken to release initial decisions and final outcomes.

The format of the decision releases had changed. Provisional opinions had started being released as status update emails instead of formal decision letters. Work was being done with committees to ensure that requests for information clearly expressed what was required from the applicants.

The HRA were working closely with colleagues in the EU for harmonisation of part II templates for documents such as the investigator CV, informed consent procedure documents, financial documents. EU guidance to support the documents was also in progress.

The HRA and MHRA were working to increase awareness and participation in the pilot.

Quotient had submitted several trials to the pilot and commented that the alignment between the MHRA and REC reviews at approval stage had worked well and meant a reduction in the number of substantial amendments required directly after approval.

Any other business

CB raised an AOB relating to the submission of IB amendments which did not impact on any other documents with the view to better understanding why they are submitted, their usefulness to the REC and regulatory impact.

The REC perspective was that the IB update only required ethical consideration if there was a change to the risk/benefit ratio. If however the change to the ratio was after recruitment had ceased, it would not require REC consideration. It was requested that, where IBs are submitted for REC review, the cover letter states why.

It was noted that some sponsors submit the IB to the REC to be on the safe side.

JM confirmed that the expectations for IB approval from a regulatory perspective was that the IB be reviewed annually but the updates do not necessarily require MHRA or REC review. Changes to the safety information should be submitted to the MHRA. If there was a resulting change to the participant information, the expectation would be that this was submitted and reviewed by the REC.

It was commented that it would be helpful if there was a tool to support sponsors and applicants in deciding who to submit which amendments too.

<u>The below information was provided by Jenny Martin post meeting:</u>

There is no one single place that covered implementing of IB or PIS updates, as we tried to consolidate and minimise rather than cover each individual doc we use the term key clinical trial documents. However, I have tried to layout how the GCP guide covers amendments and the implementation of them in particular IBs and link to PIS.

1.2.5 Implementation of amendments. Sponsor should have formalised process to document substantiality for MHRA and REC or both for that amendment. Also for the approval and implementation (general, so includes IB and PISs).

2.3.6 Covers what is considered a substantial amendment. This does not specify documents but refers to changes in the risk benefit – which would impact on the IB and PIS documents.

1.4.1 and 4.7.3 Covers updates to the IB and how this should be documented (PIS, in line with the protocol and IB).

4.3 Covers updating and amending key trial documents, including a use of a summary to easily identify changes and impact plus clear implementation.

4.5 and 6 Covers cross-checking of essential documents that contain the same or linked information. Table 4.2 column 3 clearly covers IB and PIS in safety data.

11.4.2 While this is at the investigator site and aimed at the PI, however, ultimately the sponsor has responsibility to ensure amendments are implemented correctly, so should guide the PI. On page 375 (paragraph 11 of the section) it does cover consideration of which patients should be reconsented.

So if you take these together:
The sponsor should have a robust process for change control – this includes the amendment of key clinical trial documents and any other documents linked to the one changing (so cross-checking what other documents the change impacts on or not). There should be documentation of the substantiality of the change and if it requires MHRA and/or ethics approval if substantial. There should be a summary of the change and if it is PIS consideration as to which patients it impacts on for re-consenting. Then finally evidence of when it was implemented at the site.

Action- HRA to consider the prominence of the guidance available to applicants.