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Dear Mr. Harrison,

The Harvard Multi-Regional Clinical Trials Center (Harvard MRCT), based at Harvard University, has an overarching goal of improving national and international standards for best practices in the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research clinical trials. In this capacity, we have been involved in recent discussions on return of general research results to participants. In 2014, the Harvard MRCT Center convened the Return of Results workgroup - a multi-stakeholder group comprised of 53 members from academia, industry, patient advocacy and non-profit centers. The mandate of this workgroup was to provide a practical guidance document for all sponsors (academic, industry, non-profit,) that addresses, in detail, key challenges in returning results and potential solutions. We have been working to align and harmonize approaches of multiple stakeholders (patient and patient advocates, academic, not-for-profit foundations, pharmaceutical companies, CROs, etc.) to develop approaches for participant research summaries, including the content, process, logistics, and other considerations. In addition, we have also launched a new initiative to explore solutions for Post Trial Responsibilities – an area addressed in part in the document.

Creating and disseminating general clinical trial result summaries to clinical trial participants helps to ensure that study participants are informed about the trial results, and that they understand the value of their contribution. In many cases, informed consent forms and participation information sheets (PIS) state that study participants will receive important information about the study. Return of research results helps to accomplish this commitment and to express appreciation for the study participant's time and effort. The last study visit by the participant is an important milestone for each participant and marks the beginning of a transition in care.

On September 2 2014, the United Kingdom's (UK) Health Research Authority (HRA) posted a draft document for public consultation entitled Guidance on participant information at the end of a study (Active). Harvard MRCT credits and applauds the

forward thinking that was offered in this document, the practical and clear guidance, and the careful consideration of the complexity of this process. Harvard MRCT also appreciates the opportunity to comment on a number of important areas that we think would benefit our multi-stakeholder consensus views and areas we believe need further clarification which are as follows:

1. Throughout the document, reference is made to "investigators." It would be helpful if HRA were to clarify whether the term "investigator" is used to imply only the principal investigator or more broadly to include the investigator and the sponsor. Specific clarification of the roles of the principal or site investigator and the sponsor would be useful. Many of the functions attributed to the investigator in the HRA document might be better coordinated by the sponsor of the trial; even in multi-site trials conducted by investigators, coordination by the principal investigator would appear to be preferable to each investigator deciding what to communicate.

2. *"Investigators will need to decide what the most appropriate timing is for sending out end of study information for their particular study."* Page 2

   Corporate sponsors may have particular timing considerations (e.g. to be concordant with, and not prior to, regulatory submission or disclosures to the Securities Exchange Commission and equivalent bodies) that impact the timing of disclosure. How should these functions be coordinated? We propose that the sponsor of the study communicates the anticipated timing for end of study information to the investigators in the study protocol. In the event that no sponsor exists for a clinical trial, the overall principal investigator should assume that responsibility.

3. *"In some trials, different arms of the study may have different end points and, therefore, consideration will have to be given regarding the best time to communicate with each individual patient."* Page 2

   Harvard MRCT encourages HRA to rethink whether individual patients should have different communications (timing and/or content), as this may influence ongoing studies. Concern is heightened because of the expanding use of social media as a means by which patient and advocate groups exchange information. While for many reasons transparency is welcome, in clinical trials, such transparency may significantly undermine blinded studies, data integrity and research outcomes.

4. The section on page 3 regarding requirement for ethical review appears to be contradictory. Research ethics committees (RECs) need not re-review arrangements if plans for arrangements at the end of study have been agreed upon in the initial application. If end of study plans "contradicts" previous

approved information, then resubmission to the REC may be required. However, bullet 3 states "There is no need to seek to REC review of the end of study information sheet simply because you did not reference the end of study information sheet in the initial documentation reviewed by the REC. Similarly, any material used for the dissemination of the study findings should not be submitted for ethical review." Thus, if no mention is made at the outset, then the REC need not review the material. This paragraph seems contradictory to the first, and would profit from clarification.

5. "What happens when the study stops"? Page 4 details
    a. *"The arrangements for treatment after a therapeutic trial must be spelt out."*
        i. What if there are no specific treatment options for the participant? What is the responsibility of the investigator and of the sponsor? We suggest this be amended to "The arrangements if any, for treatment after a therapeutic trial must be spelt out."
        ii. What is the responsibility if the participant does not have access to usual care?
    b. *"If a significant clinical effect has been observed there may be plans to offer the treatment to those in the placebo or control arm as well. If the treatment will not be available after the research finishes, you should explain to the participant and provide information on what treatment will be available instead."*
        i. Harvard MRCT strongly recommends referral to or back to a treating physician or caregiver as opposed to the investigator (should they be different) to determine which treatments are otherwise available for the condition of study.
        ii. The expectation described in this paragraph expands the ethical responsibility of the investigator significantly from current practice, particularly when the investigator may not be the most appropriate person to discuss and explain available options to the participant. Moreover, there is no distinction between such a responsibility and the particular circumstances, for example, whether the trial involves a serious or life-threatening conditions, chronic disease or otherwise.
        iii. We suggest this sentence be amended to "If a significant clinical effect has been observed there may be plans to offer the treatment to those in the placebo or control arm as well. If the treatment will not be available after the research finishes, you should explain that to the participant and provide information on what treatment if any, will be available instead."
    c. *"Different information may be required for different sub-groups of patients."*

   i. There are practical concerns if different groups of participants are given different information, and if the information differs between investigators.

d. *"Arrangements for further treatment / access to the study intervention beyond the end of the study should match those set out in the original PIS. Arrangements which conflict with the original PIS will require further ethical review."*

   i. The original PIS may not anticipate the end-of-study results and therefore benefits and options. Thus, it would appear that either the original PIS will be extraordinarily complicated, or ethical review will be necessary after revision for many clinical trials. The practical implications and feasibility should be considered since ethical review is unlikely to coincide with end of study visit.

6. "[P]articipants have an expectation that they will be given access to the results of a study and investigators should normally provide them." Page 5

   While the later paragraphs allow for the use of video presentations and other methodologies, Harvard MRCT believes that it would be helpful explain HRA's reasoning underlying the preference for investigator disclosure and perhaps even more importantly, encourage the exploration of other avenues that would similarly meet the needs of study participants. For instance, industry sponsors might create a password-protected patient portal containing updates as to when the collection of data and analysis will be complete, an appreciation or "thank you" an opt-in to receive summary results, language preference, others who may be contacted and how. Alternative methods of communication will need to be offer to those who do not have access to the internet including paper version through postal service if needed.

7. *"Study results to be given to participants should be made available in summary form. However, you may also want to inform participants how to access the results in more detail at a later stage if they so wish."* Page

   Sponsors are developing processes and content to provide plain language summaries. As a first step, providing this summary data will better meet the needs of patients. Providing access to further detail will necessarily need to incorporate many of the learnings and best practices of this first step together with an increased understanding of potential untoward consequences before moving into a later step of providing greater detailed or individual data.

8. *"[I]nformation may be staged as [it] becomes available."* Page 6

Similar to what has been stated in other sections, Harvard MRCT is concerned about the feasibility, logistical challenges and resource expectations of such an approach.

9. *"It is likely that a considerable period of time may elapse before it is possible to break the code and so participants should be made aware of the likely timing so that they know when and how to expect this information."* Page 7

   Participant may have interest in ascertaining to which study arm they were assigned. Harvard MRCT questions whether the randomization code is likely to be available at some time other than after data completion and results reporting. There are also concerns about impacting on-going research in the same study or other studies involving the same medicine or disease.

Harvard MRCT suggests that HRA reconsider the detail and specificity of the information expected to be provided. We think that a more practical approach would be to ensure that the participant is referred back to the treating physician for counseling regarding options for receipt of follow-up clinical care. The following items were developed by Harvard MRCT's multi-stakeholder workgroup and may be of interest to HRA to the extent they overlap or add new insights to the HRA Guidance for Researchers:

- Information as to what patients should anticipate once their participation ends and advice regarding monitoring for adverse events, both anticipated and unanticipated, if appropriate. In the event of questions, or adverse events, who to contact and the appropriate contact information.
- A reminder, if appropriate, that the participant may be contacted in the future if any adverse events are uncovered that might impact their health.
- Access to any benefits or care as a consequence of participation, if any, should be explained.
- Advice as to where to obtain further treatment and/or clinical care, particularly in the event that the participant does not have a health care provider.
- Any information regarding the participant's personal data developed during the study (see below).
- Whether the participant would or would not like to receive aggregated study results at end of study.
- If the participant has opted to receive the plain language summary, how to access the information and when to anticipate the information will be available.
- Ensure that the participant has the ability to access the results in the format provided (e.g. literacy if the results will be written, internet access if results will be posted).[1]
- Contact information for the participant, if appropriate.

[1] Indeed, sometimes the method of delivery will impact the participant desire to opt-in (e.g. participants may not wish to receive a letter at home).

- Whether the participant would like to designate a third party to receive results in the event of their incapacity or death.
- The HRA draft guidance denotes this activity as “reporting of side effects” p. 5. We suggest that the more general term “adverse event” be utilized as the term “side effect” is typically used for marketed products only and connotes a causal relationship as opposed to an association not yet attributable to the study medicine.

We appreciate the opportunity to comment and to offer our perspectives. We think it would also be helpful to guide investigators and sponsors as to how to approach individuals who “drop out” of clinical studies, but are nevertheless interested in learning of the results. Further, certain “special considerations” might be addressed such as studies that close early due to efficacy, futility or low enrollment; observational, long-term or follow-up studies; vulnerable populations; child assent; return of results in the event of a participant death; and studies that do not warrant return of results.

It is critical to coordinate efforts to return aggregate results globally and to harmonize regulations within the government across all agencies and across governments internationally. Most clinical trials are multi-centered, multi-national, and often global. Different regulatory expectations and requirements will hamper and complicate well-intentioned efforts to communicate with and engage participants and the public. International guidelines and specific tactical and logistical recommendations should be coordinated and adopted.

With the goal of increasing transparency, ensuring that participants are informed of the results of studies in which they participate is both appropriate and but also respectful. While return of results may be resource intensive, methods are available that are relatively low cost, feasible, and straightforward; at a minimum, employing these utilitarian methods –even if not ideal in all populations and in all locations—will respect participant privacy and individual choice, and may result in greater public engagement and trust in the research enterprise. We sincerely appreciate the attention that HRA has paid to addressing this need.

Very truly yours,

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On behalf of the Multi-Regional Clinical Trials Center of Harvard University