Response of MHRA to Preventing Future Deaths Report

Coroner's Officer [redacted] received the following email from MHRA 23rd October 2022 in response to a Regulation 28 made by Assistant Coroner for Derby & Derbyshire, Miss Sophie Lomas.

From: MHRA Customer Services
Sent: 23 October 2022 11:51
To: [redacted] (Corporate Services and Transformation)
Subject: CEC 113283 Reg 28 Report - After Inquest DRAPER R 13022020

Our Reference CEC 113283

Dear [redacted]

Thank you for your email dated 4th August 2022.

Apologies for the delayed response.

The MHRA propose that no action is required in relation to either of the matters of concern raised. A detailed response is provided for each point explaining the systems in place for unblinding of clinical trials and the responsibilities for executing those processes.

1. **There is a lack of a clear system and protocol on whose responsibility it is to trigger consideration of the unblinding process and the correct procedure that should be followed by the treating hospital. If such a protocol in fact exists, then it does not appear to have been sufficiently disseminated.**

Contact with the trial team is reliant on the patient informing the treating physician that they are enrolled on a clinical trial by providing the patient card, patient information sheet or investigational medicinal product packet, to them. Patients are told that they should do this as part of their enrolment in the trial. Provision of this information to the treating physician allows them to contact the trial team and request unblinding of the patient if this is deemed necessary for the immediate management of the patient. The decision to unblind sits with the treating physician at the time of the emergency event but requires contact to be made with the Principal Investigator responsible for the trial participant (or an appropriately delegated member of their team) in order to unblind the trial treatment. It is expected that the investigator site has the ability to unblind a trial participant immediately in the case of a medical emergency.

The MHRA has published the following information in the MHRA Good Clinical Practice Guide (2012) – section 11.4.8 Contact Details and Out-Of-Hours Arrangements and 11.4.9 Emergency Code Breaking:

There are a number of methods by which trial subjects are provided with the contact details of the research team, including wallet-sized subject cards and information contained on the site-specific sections of the subject information sheet. This information permits the subject to contact site staff in the event of questions arising or to notify them of adverse events or issues that have arisen.

This information may also be used if the subject is seen at another hospital (for example, in an emergency situation), to access additional information about the trial or to access code-breaking processes. It is therefore imperative that systems are in place to facilitate this contact. The three most commonly used methods of contact are described below:

- **Investigator's office number** This number is suitable during hours when the office is manned, but arrangements should be in place to forward the call to an alternative number or to provide additional contact details on the voicemail.
- **Ward or switchboard landline number** This arrangement has the benefit of the number being permanently manned. However, arrangements need to be made to ensure that staff taking the call are aware of the trial and the out-of-hours arrangements, and either have access to trial information so that the call can be handled appropriately (this may be suitable if there is a large trial team providing 24-hour coverage), or hold trial team personal contact information. There should be alternative back-up contacts if the nominated person(s) are unavailable.
- **Trial-specific or personal mobile phones and pagers** These are commonly used, but care should be taken that an appropriate voicemail message is left, as described above. If callers are asked to leave a message rather than being referred onwards to an alternative contact (for example, how long to await a call-back before trying an alternative contact) then frequent checks for received calls should be made by the mobile phone holder.

Whichever system is used for cover, it should be assessed and tested accordingly to ensure that the chain of contact functions as intended. Out-of-hours arrangements for trials that are hospital based, such as in an oncology unit, tend to be routinely challenged on a daily basis and subjects are usually well trained to contact their trial team out of hours if they become unwell after they have received a course of chemotherapy. Higher-risk areas are when the out-of-hours arrangements are not routinely used and the medically qualified doctors responsible for the out-of-hours service are not familiar with the trial (for example, where out-of-hours cover for a GP surgery is contracted out to a third party provider). Investigators and sponsors need to assess the suitability of these out-of-hours service providers prior to use. Another additional factor for determining frequency and extent of out-of-hours arrangements is whether the trial is blinded or open. The process for unblinding should be clearly defined and tested when non-trial personnel are involved in providing out-of-hours medical cover.

Appropriate arrangements should also be in place to ensure that there is cover for those staff who are travelling (and therefore may not have access to the information and systems required), and for staff who are on holiday or on sick leave, to ensure that access to the trial team and code-breaking arrangements are maintained at all times.

There are various methods available for the unblinding of trial subjects should this become necessary in an emergency: for example, to manage the treatment of a subject following an SAE. Most of these methods are dependent on the investigator site to manage the process,

although back-up arrangements may exist through the sponsor. Prior to initiating the blinded clinical trial at their site, the PI should therefore ensure that a robust unblinding process has been implemented; that either the code breaks are on site in a designated place or working access codes for the IRT have been provided; and that all staff involved in the trial and process are aware of the arrangements. Consideration should be given to testing the code-break process if it involves a number of steps or staff (this testing is sometimes combined with the testing of the out-of-hours process). Any testing must be documented and retained as evidence that it took place, and either that it is satisfactory, or if not, that corrective action has taken place.

If a code break is needed to permit the appropriate medical management of a subject, the reason for the code break and the circumstances should be clearly documented (for example, in the hospital notes, in code-break envelopes, in the IRT system or on a specific form) and communicated to the PI and sponsor at the earliest opportunity. Care should be taken to limit the knowledge of the randomisation arm the subject was assigned to, in case this could affect the blinding of other subjects or future trial assessment of the subject (for example, analysis of samples or scoring of questionnaires, categorising of adverse events).

Prior to approval by the MHRA, all clinical trial applications are reviewed by a multi-disciplinary team of assessors. For double-blind trials, part of the medical assessment is to ensure that an appropriate process for unblinding is in place and is adequately described in the trial protocol.

It should also be noted that the IMP packet would also include the name of the Principal Investigator and contact details of the hospital which issued the medication so a treating physician could potentially access additional information about the trial by contacting the investigator site pharmacy department which could then be passed to the trial team (although for this trial the patient would not have been in receipt of the medication as it was administered at the hospital). It is however possible that certain information can be omitted from the label if it is contained within the patient information sheet or patient card (as described in Annexe 13 ‘EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use‘

The HRA has published guidance relating to contact with the PI (consent and participant information guidance) which states that participants should be provided with the following contact information:

- *Specific information about this research study: usually this would be provided by someone who is part of the research team; this could be you or some other member of your team. Potential participants should be given a name and contact details. If you also have a study website, details of where to find this should be included.*
- *Who they should approach if they are unhappy with the study: this would be a contact if participants have any concerns about your study and their involvement in it. For some studies, you may need to provide an emergency contact number that is manned 'out-of-hours'.*
- *The HRA have also published the CTIMP protocol template which provides guidance about the responsibilities for emergency unblinding and what should be included in the protocol in section 7.5. It is published in the templates section of the following webpage: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/*

2. **There is no formal referral system for the treating hospital to use to report adverse events to the trials team and trigger consideration of the unblinding**

process. This means that conversations about the process between hospitals are not transparent.

As described above, the mechanism is that the patient notifies the treating physician that they are on a clinical trial and provides the contact details of the trial team via the patient information sheet, patient card or IMP packet. The treating physician can then contact the trial team using the provided details in order to obtain any required information.

- Please find attached a copy of the (ATOMIC-Meso Phase 2/3 Study) patient information sheet which is to be completed by the investigator site and provided to each trial participant as part of the informed consent process. The patient information sheet contains a space for completion of the name of the Principal Investigator, their contact details and a 24-hour emergency number. Participants are informed that they may contact the PI and the study staff at the numbers provided with any questions about study-related injuries or if they have any questions or concerns about the study. They are also told to 'tell the study doctor immediately if you are injured or become sick as a direct result of taking part in this study'.
- Please also find attached a copy of the template patient emergency ID card which was submitted to the research ethics committee as part of the (ATOMIC-Meso Phase 2/3 Study) trial documentation. The trial participant is told to keep the card with them and provides the emergency contact details for the trial participant/ treating physician to contact to obtain further information regarding management of treatment in the event of an emergency or treatment complications.

It is expected that the Principal Investigator (or delegated member of their team) appropriately document any contact with a physician treating a participant for which the PI is responsible especially where this contains discussion of treatment options or requests for unblinding so that this can be verified. It would be common practice for the treating physician to also document any attempts to contact and the outcome of any conversation in the patient's medical record as part of routine clinical care expectations.

Please note Health Research Authority, HRA only provided the tracked changes in the PDF version attached.

With regards

[redacted]

MHRA Customer Experience Centre

Communications and engagement team

Medicines and Healthcare products Regulatory Agency

[redacted]

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