Pandemic Situation
Questions and Answers

1. Protocol Amendments

Will there be any leeway for implementation of minor amendments in the event of reduced MHRA capacity?

Non-substantial amendments do not need to be reported to the MHRA before being made. Substantial amendments should be notified to the concerned Ethics Committee and the MHRA in the normal way. It is very difficult to predict the impact on clinical trial activity during a full pandemic situation as it will be complicated by trial staff being re-deployed to assist with core healthcare activities, as well as potential illness amongst the trial teams and the trial subjects. Where trial activity continues we would expect Sponsors to continue to meet their obligations with respect to clinical trials legislation, guided where necessary by advice from our website and from our helpline, as the situation develops.

Does a temporary halt in trial need to be notified during a pandemic?

Yes, we would expect Sponsors to continue to meet their obligations with respect to clinical trials legislation, guided where necessary by advice from our website and from our helpline, as the situation develops.

2. Investigational Medicinal Product

Our IMP supplies are approaching expiry and we are unable to resupply. What should we do?

This will be trial specific. Contingency plans should be in place to minimise the impact on patient safety and data integrity. All protocol deviations should be recorded in the CRF, and serious breaches recorded for reporting when the situation allows this to be done. If this situation results in a temporary halt to the trial whilst alternative sources are being investigated or even early termination of the trial, we would expect Sponsors to continue to meet their obligations with respect to clinical

trials legislation, guided where necessary by advice from our website and from our helpline, as the situation develops.

Should we follow the same process for re-labelling due to an extension of shelf-life during a pandemic?

Yes, we would expect Sponsors to continue to meet their obligations with respect to Annex 13 (42), to ensure the process is adequately controlled and documented. The legislation already has an element of flexibility, in that the re-labelling can be carried out by, or under the supervision of a clinical trial pharmacist, or health care professional.

Is it acceptable to resupply using site to site transfer during a pandemic?

Annex 13 (47) already allows for site to site transfer by exception as in a pandemic situation. We would expect the Sponsor to have appropriate standard operating procedures in place to ensure adequate control of the process and full traceability. The product history while outside the control of the manufacturer and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Qualified Person should be sought. The need for re-labelling should also be considered as this may require the product to be returned to the manufacturer and certification by a Qualified Person.

We need to re-supply from a different source due to the pandemic. What should we do?

A change to the source of supply would be considered as a Substantial Amendment which should be notified to the concerned Ethics Committee and the MHRA in the normal way.

Can clinical trial stock e.g. comparators be re-used for critical out of stock situations?

This will be trial specific and re-supply should be the exception and would be dependent on whether the integrity of the product can be verified. We would expect the Sponsor to have appropriate standard operating procedures in place to ensure adequate control of the process and full traceability. The product history, storage

conditions, potential for contamination/adulteration, etc. while outside the control of the trial site should be reviewed as part of the assessment of the product's suitability for re-supply and the advice of the Clinical Trial Pharmacist and/or Qualified Person should be sought.

Do records of accountability need to be maintained during a pandemic?

Yes, we would expect Sponsors to continue to meet their obligations with respect to clinical trials legislation by ensuring full traceability records are maintained.

3. Safety Reporting – SUSARs and ASRs

We have received reports of AEs/SAEs from our trial subjects relating to flu medications (e.g. Tamiflu). Should we report these to the MHRA?

Yes, the MHRA has developed a special web based system for reporting suspected side effects to Tamiflu and Relenza - the swine Flu Adverse Drug Reaction (ADR) Portal - which can be used to report such events (http://swineflu.mhra.gov.uk).

A number of our trial subjects have flu and are reporting flu related AEs/SAEs. Do we have to record all of these on the CRF?

Yes, unless the Sponsor can justify a substantial amendment to the protocol which excludes reporting this type of event. The amendment would require approval by CTU and the appropriate REC.

Do you expect Sponsors to continue to report SUSARs according to the existing timelines in the event of a pandemic?

Yes, we would expect Sponsors to continue to meet their obligations with respect to clinical trials legislation, guided where necessary by advice from our website and from our helpline, as the situation develops.

Do we still need to submit ASRs during a pandemic?

Yes, we would expect Sponsors to continue to meet their obligations with respect to clinical trials legislation, guided where necessary by advice from our website and from our helpline, as the situation develops.

4. Protocol adherence

Trial patients are taking flu meds that are excluded by the protocol. What should we do?

This will be trial specific. Contingency plans should be in place to minimise the impact on patient safety and data integrity. All protocol deviations should be recorded in the CRF.

Key medical examinations (ECGs, labs etc) cannot be obtained as required by the protocol for entry/continuation/dose escalation/dose reduction. What should we do?

This will be trial specific. Contingency plans should be in place to minimise the impact on patient safety and data integrity. All protocol deviations should be recorded in the CRF. At the point of reporting, publication or submission due consideration to all deviations should be given to the impact on the data integrity, as well as the safety of the patients and product safety profile.

A number of our trial subjects are not turning up for their scheduled follow-up visits. What should we do?

This will be trial specific. Contingency plans should be in place to minimise the impact on patient safety and data integrity. All protocol deviations should be recorded in the CRF. At the point of reporting, publication or submission due consideration to all deviations should be given to the impact on the data integrity, as well as the safety of the patients and product safety profile.

5. Monitoring

Do you expect Sponsors to continue to monitor trials at the same frequency in the event of a pandemic?

It would be important for Sponsors to produce contingency plans for monitoring where a pandemic severely reduces monitoring resource e.g. when it considered too dangerous to send monitors to sites. Consideration should be given to other means of verifying compliance with activities critical to subject safety or to data integrity. Central monitoring methods may be of benefit.

6. Record keeping

What level of documentation is required during a pandemic situation?

Trial organisations should keep a record of any deviations, breaches etc. that occur, along with the reasons for them happening. This record keeping is to allow a thorough review of non-compliance, once situations return to normal. At the point of reporting, publication or submission due consideration to all deviations should be given to the impact on the data integrity, as well as the safety of the patients and product safety profile.

7. MHRA review and approvals

Is there any guidance on the regulatory impact of reduced monitoring and medical support, on data acceptability for approvals?

Greater weighting and prioritisation should be given to the safety of trial subjects/patients. For example, if resource for monitoring or IMP control is drastically reduced, the remaining resource should be prioritised on those trials where the consequences for patient safety are greatest. If protocol, GCP, or SOP deviations affect lower (patient) risk trials, as a result of pandemic problems, even if those trials are intended for MAAs, then it would be sufficient to record the deviations in the clinical trial reports. Serious breaches of compliance should be reported in the usual way, although MHRA may relax its expectations of reporting times, during a serious pandemic situation.

What will be the impact on review and approval of CTAs and substantial amendments by the MHRA in the event of a pandemic?

It is very difficult to predict the impact on MHRA activity during a full pandemic situation, however, contingency plans are in place to ensure as full a service can be provided as is possible. Sponsors are encouraged to refer to our website on a regular basis for up-to-date advice and information.

8. Serious Breaches

We believe we have identified a serious breach but due to the pandemic we cannot obtain sufficient information to report within the timelines. What should we do?

Serious breaches should be recorded for reporting when the situation allows this to be done. Action as necessary for the safety of trial subjects should be implemented and recorded as an urgent safety measure or within the serious breach report.

9. SOP deviations

Will it be acceptable for Sponsors to draft Planned Deviations from relevant SOPs, e.g. PI vs nurse authority, monitoring frequency, protocol deviations?

We would encourage trial organisations to consider the impact of a pandemic on their processes. If contingency measures are being produced for pandemic situations, they could be incorporated, appended, or linked to current SOPs. That way the organisation will not be deviating from their SOPs when the contingency measures are required.

10. Business continuity

Should Sponsors develop contingency plans, which include consideration of Business Continuity issues, specifically for a pandemic situation?

Yes, this is recommended and such plans may be examined during GCP inspections. The factors discussed above relating to risk assessment for monitoring activities, the use of USMs, flexibility relating to the reporting of serious breaches and maintaining an audit trail of decisions should be covered in a contingency plan, as well as issues relating to how to maintain business-critical IT systems.