TMQA Regulatory News Update August 2017

MHRA Issues GCP Inspection Metrics Report

On 21 July 2017, the MHRA issued their GCP inspection metrics report covering the period from 01 April 2015 to 31 March 2016. During this period, a total of 102 GCP inspections were performed by the GCP Inspectorate, which included the following: non-commercial organisations (19), commercial sponsors (13), Contract Research Organisations (CROs) (8), investigator sites (29), phase I units (10), UK laboratory facilities conducting clinical trial sample analysis (8), and non-UK and EMA inspections (15); the latter included 7 EMA and 8 non-EMA foreign bioequivalence inspections. Of these inspections, 22 were triggered inspections in response to, for example, a serious breach report.

A summary of some of the findings from these inspections is provided below:

- Commercial sponsors – of the 10 inspections, 3 had at least one critical finding and 8 had at least one major and/or critical. The critical findings related to the following:
    - Data integrity - the sponsor had received a critical finding at their previous inspection in 2013 for data integrity, relating to use of electronic patient diaries (EPDs). The follow-up inspection revealed that many of the same issues remained, for example: 562 data queries had been raised on patient reported data in 3 trials and the majority of the requested changes were accepted by the sponsor, although there was insufficient source data to support the changes; there was insufficient documentation of user acceptance testing (UAT) for the EPD – the UAT plan had not been approved and it was not evident who had performed all of the UAT; reviews of edited EPD data had not taken place on a monthly basis as required by study plans; CAPA commitments to the previous inspection relating to written procedures covering the data query process had not been adequately fulfilled; there was a failure to detect and monitor user assignments to the database that contained patient reported data, eg. inappropriate staff had been given Principal Investigator use rights; IMP dosing calculation errors had not been detected during monitoring or data cleaning.
    - Data integrity – this was given for 2 reasons: (1) ineligible patients had been included in the per protocol analysis population for 2 trials and processes used to determine how a deviation would be classed as major/minor were not defined anywhere; (2) the audit trail from the interactive response technology (IRT) systems for both trials was not made available during the inspection and when it was provided, there was no time stamp of the actions taken by users. The IRT validation documentation had no evidence that the secondary endpoints scores that were calculated by the IRT system had been validated.
    - Essential documents/Trial Master File (TMF) - the TMF presented as a hybrid paper and electronic TMF to the inspectors did not meet legislative requirements and, as a result, impeded inspectors from assessing GCP and legislative compliance. There was a particular issue with product and trial level documents.

The highest percentage of major findings (ie. >10%) from inspections of commercial sponsors related to record keeping/essential documents, pharmacovigilance and archiving.

- CROs - of the 8 inspections, none had any critical findings but all 8 had at least one major finding. The highest percentage of major findings (ie. >10%) related to quality system, record keeping/essential documents and computer systems validation.
- Non-commercial organisations – of the 20 inspections, 8 had at least one critical finding and all 20 had at least one major finding. The critical findings related to the following:
    - Principal Investigator oversight – the contact between the NHS Trust sponsor and the Chief Investigator (CI)/Principal Investigator (PI) had expired and while this was being resolved, trial recruitment was halted but notifications were not made to the MHRA or Research Ethics Committee. The CI/PI left the NHS trust but was still acting as CI/PI, but with no contact. Additionally, the review of inclusion/exclusion and eligibility decision was not documented in the patient notes, but completed in the case report form by the research nurse after randomisation.
    - Pharmacovigilance – 2 critical findings related to pharmacovigilance:
        - There was significant potential for Suspected Unexpected Serious Adverse Reactions (SUSARs) to go unreported through a number of failing processes including: the Reference Safety Information (RSI) for all trials using the Summary of Product Characteristics (SmPC) was being updated without an amendment being sent to the MHRA or any assessment of new expected terms being carried out; there were no processes in place to ensure that the Investigator Brochures that contain the RSI were reviewed on an annual basis and the Trust were unaware of this requirement.
        - There were several issues with RSI. For example: trial teams were unaware that substantial amendments relating to RSI need to be approved by the MHRA and research ethics committee prior to implementation; there was evidence of new RSI versions implemented without MHRA or research ethics committee approval and the impact of patient information sheets was not assessed; the SmPCs were being used for both trial IMPs, whereas it was the IB that had been submitted to the MHRA in the initial clinical trial authorisation application; RSI was not clearly defined for a trial as there was insufficient assessment to determine whether the RSI was suitable for the trial population. Other pharmacovigilance issues, aside from RSI included: an example was seen of a SUSAR relating to the miscarriage of the pregnancy of partner of a male trial participant that was not reported to the MHRA; events were missing from the Development Safety Update Report (DSUR); issues were seen with the inadequate completion of SAE reports; there were multiple errors in the SAE listings for the selected trials provided to the inspectors prior to the inspection.
    - Essential documents/TMF – both sponsor and investigator files for a TMF that was selected for inspection had been lost and were therefore unavailable as the basis for the inspection. As a result, there were no CRFs available or the ability to identify patients and therefore the source data that supports the publication of the trial results.
    - Sponsor oversight – 3 critical findings related to sponsor oversight:
        - There was a lack of a formal quality system and as a result, no processes to cover key sponsor responsibilities such as: protocol and amendments review and approval, serious breaches, urgent safety measures, TMF and archiving,

monitoring, pharmacovigilance requirements, vendor selection, training and data management.

- The university had sponsored and co-sponsored a number of clinical trials since 2008 and in 2013 the need for formal processes to cover granting sponsorship and oversight of Clinical Trials of Investigational Medicinal Product (CTIMPs) was identified. However, no action had been taken to implement processes.
- The majority of sponsor oversight was performed as remote activities which were not adequately defined or documented and therefore resulted in serious breaches notified to the MHRA.

- Data integrity – 2 critical findings related to data integrity:
  - Systems and processes examined during the inspection and observations made cast doubt on the reliability of the data in the database and consequently the trial results. For example: changes were made to the database prior to investigator approval and there was inappropriate use of self-evident corrections; lack of QC of data entry from paper CRFs; complete absence of key source data at site.
  - Source data verification by the inspectors of 3 patients identified numerous inaccuracies with the trial database resultant from unclear data entry guidelines, database field issues, and untimely entry/correction of source data. None of the patients reviewed had a completely accurate data set in the database. There had been no on-site monitoring by the sponsor. Additionally, the source documentation for IMP administration was unreliable.
- Subject Eligibility – in one trial there were 6 eligibility violations but the subjects were enrolled in the trial as waivers. These were identified retrospectively by the sponsor following completion of the trial. In another trial, a subject's body mass index of 29.98 had been rounded up to 30 to allow the subject onto the study. The sponsor's processes failed to ensure the eligibility violations were identified, assessed and escalated in a timely manner.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/631254/GCP_INSPECTIONS_METRICS_2015-2016__FINAL_21-07-17_.pdf

EMA Issues Press Release Related to Brexit

The European Medicines Agency (EMA) issued a press release on 1 August 2017 on the business continuity plans being implemented as a result of Brexit. The business continuity plan aims to deal with the uncertainty and workload implications linked to the UK's withdrawal from the EU and the relocation of the EMA. The plan sets out three layers of priority, according to their impact on public health and the EMA's ability to function. In May, the EMA started to scale back activities in category 3 activities (lowest priority), to free up 43 staff by the end of 2017 who are focusing on the UK's preparations for withdrawal from the EU and EMA's relocation. To achieve this the EMA decided to temporarily suspend a number of activities including:

- The development of the European Medicines Web Portal, a new publicly-available online information source on all medicines marketed in the EU;
- EMA's contribution to the e-submission project that will participants to electronically submit documents linked to authorisation requests for human and veterinary medicines in a secure and efficient way;

- The development of a transparency roadmap for EMA that lays out future transparency measures of the EMA and;
- Participation in the benchmarking of medicines regulatory authorities in the EU as of 2018.

In addition, the EMA reduced the number of audits as well as some corporate governance and support activities. Participation of EMA staff in external meetings or conferences has been reduced, as has the organisation of EMA meetings and workshops. Further iterations of the business continuity plan will also take into account various scenarios for staff losses and how these may affect the delivery of category 1 and category 2 activities. Unexpected higher, faster or more permanent loss of staff as a consequence of the EMA's relocation may lead to a situation in which the EMA's operations can no longer be maintained. The EMA will provide further updates on the implementation of its business continuity plan as necessary.

A transcript of the speech given by Lord O'Shaughnessy on Brexit and medicines regulation, at the 2017 MHRA/BIA Conference on 14 July 2017 has been published on the MHRA's website. In relation to medicines regulations, Lord O'Shaughnessy stated that, in the event that it is not possible to reach a deal that secures ongoing, close collaboration between the UK and Europe, the UK will set up a regulatory system that is robust, efficacious and does not impose any additional bureaucratic burdens.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002789.jsp&mid=WC0b01ac058004d5c1

EMA Issues Revised Guideline on First-in-Human Trials

The EMA issued revised guidance in July 2017 on first-in-human (FIH) clinical trials to further help stakeholders identify and mitigate risks for trial participants. The guideline was adopted by the Committee for Medicinal Products for Human Use (CHMP) on 20 July 2017 and comes into effect on 01 Feb 2018. This is the first revision of the "Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products". It extends the existing EU guidance to address FIH and early phase clinical trials with integrated protocols. The revision takes into account the fact that in the past 10 years trial protocols have become increasingly complex and now often include different parts within a single clinical trial protocol, aimed at assessing, for example, single and multiple ascending doses, food interactions or different age groups. The revision is intended to further assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new investigational medicinal products. The document includes considerations on quality aspects, non-clinical and clinical testing strategies, study design and conduct of FIH/early clinical trials. Strategies for mitigating and managing risks are given, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002783.jsp&mid=WC0b01ac058004d5c1

New Draft GVP Guidance Issued

A new draft guideline on good pharmacovigilance practices (GVP) was released for public consultation by the EMA on 02 August 2017. This new GVP is module IV "Product- or Population-Specific Considerations IV: Paediatric Population". The consultation period for this module ends on 13 October 2017 and the anticipated date for coming into effect is Q1, 2018. New pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) came into force in the EU in July 2012, providing for strengthened pharmacovigilance processes for all medicines, irrespective of their

authorised indication(s) and population(s). This new legislation introduced changes that are particularly relevant for the paediatric population, in particular the extended definition of adverse reaction – to include harm resulting from overdose, misuse, abuse and medication errors – and the related broadening of the scope of pharmacovigilance to include evaluation of risks associated with medicines when used outside the terms of the Marketing Authorisation, including "off-label use". Subsequent to the changes in the scientific and regulatory environment, the "Guideline on the Conduct of Pharmacovigilance for Medicines used by the Paediatric Population (EMEA/CHMP/PhVWP/235910/2005 – rev.1) needed to be updated and the revised guidance is now provided in this Product-Specific Considerations Chapter P.IV of GVP. This guidance should therefore be read in conjunction with Title IV of the Paediatric Regulation and its Article 34, Regulation (EU) No 726/2004 and Directive 2001/83/EC. The guidance contained in this Chapter is addressed to marketing authorisation applicants and holders, the competent authorities in Member States and the EMA. It covers all paediatric ages groups and should additionally be of interest to both parents/carers, healthcare professionals, patient/consumer organisations of national healthcare systems in Member States.

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232769.pdf

New Confidentiality Commitment Strengthens EU-US Cooperation in Medicines Inspections

The European Commission (EC), the US Food and Drug Administration (FDA) and the EMA have signed a new confidentiality commitment that allows the FDA to share non-public and commercially confidential information, including trade secret information relating to medicine inspections with EU regulators. The confidentiality commitment is the most recent step in the ongoing implementation of the mutual recognition of inspections of medicines manufacturers , which was announced in March this year following years of collaboration and aims to strengthen ties between the EU and US. The EU and US have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific processes. However, complete exchange of information was not possible under these arrangements. The new confidentiality commitment formally recognises that the FDA's EU counterparts have the authority and demonstrated ability to protect the relevant information. This now allows sharing of full inspection reports, allowing regulators to make decisions based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/08/news_detail_002800.jsp&mid=WC0b01ac058004d5c1

MHRA Updates List of Phase I Accredited Units

On 28 July 2017, the MHRA updated their list of phase I accredited units. The list includes 14 accredited phase I units in the UK – 10 in England, 2 in Northern Ireland, 1 in Scotland and 1 in Wales. The MHRA phase I accreditation scheme is a voluntary scheme for organisations conducting phase I trials, in particular those conducting first in human trial. Organisations in the scheme have to exceed the basic regulatory good clinical practice standards by having additional procedures that include the highest standards for avoiding harm to trial subjects and for handling any medical emergencies.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/634146/List_of_accredited_units__28_July_2017_.pdf

Single IRAS Form is Adopted UK-Wide

A combined Integrated Research Application Form (IRAS) form that merges the Research Ethics Committee (REC) and R&D forms is now being used across the UK. Following its successful use for projects where the lead NHS R&D office is based in England, the single IRAS form should now be used for projects where the lead NHS/Health and Social Care (HSC) R&D office is based in Northern Ireland, Scotland or Wales. Adoption of the single IRAS form UK-wide from 28 June 2017 will save time and effort for applicants and sponsors and help build UK-wide consistency. For projects led from Northern Ireland, Scotland or Wales, although a single form replaces the separate REC and R&D forms, this single IRAS form will continue to be separately submitted for ethical review (where applicable) and review against NHS/HSC standards as per current process.

http://www.hra.nhs.uk/news/2017/06/21/combined-iras-form-replaces-separate-ethics-rd-application-forms-uk-wide-basis/