New WHO statement on disclosure of clinical trial data calls for more transparency

The World Health Organization (WHO) has entered the ongoing debate about the publication of clinical trial data, by issuing a public statement that calls for the disclosure of results from clinical trials regardless of their findings. The statement requires clinical trial results to be publicly reported within 12 months of the end of the trial, and also highlights the need for the results of previously unpublished trials to be made publicly available. Observers note that providing public access to such data should ensure that all stakeholders – including patients, clinicians and payers – can make fully informed healthcare decisions. See page 2 ►

CIRS finds improvements in regulatory efficiency

The pressure on pharmaceutical companies to bring valuable new products to the market as quickly as possible is well documented. The final step in the process – regulatory review – is largely outside the control of sponsors, but regulatory agencies are also keen to achieve efficiencies. The Centre for Innovation in Regulatory Science (CIRS) monitors regulatory performance and has recently analysed trends in the approval of new medicines over the period 2004–2013 for the regulatory authorities in Australia, Canada, the EU, Japan, the USA and Switzerland. Further information on page 4 ►

Good practice guides aim to prevent medication errors in the EU

Medication errors are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient. All adverse reactions resulting from medication errors in the EU must be reported to EudraVigilance. In an effort to raise awareness of the legal requirements for stakeholders involved in the reporting, evaluation and prevention of medication errors, the European Medicines Agency has issued two new draft good practice guides. Comments are invited by 14 June 2015. Learn more on page 5 ►

HRA defines end of study information for trial subjects

The UK’s Health Research Authority (HRA) has issued a guidance document describing the information that should be provided to subjects when their participation in a clinical trial comes to an end. While the initial informed consent documentation outlines general plans for ongoing care at the end of a trial, more specific details may become available later in the trial. The end of study information sheet is therefore an opportunity to update the information provided to subjects and to reassure them about what will happen next. More on page 3 ►

GCP lessons: subjects receive incorrect trial drugs

Investigational medicinal products (IMPs) should ideally be prepared and dispensed by a pharmacy. However, there are often genuine practical reasons for the investigator (or another appropriately qualified member of the trial team, as detailed in the delegation log for the trial) taking on this responsibility. While this is an acceptable practice under GCP, it is imperative that the investigator is thoroughly familiar with all dispensing procedures and drug accountability requirements in order to minimise the risk of medication errors. Any deviation from the established procedures could result in a subject receiving the wrong IMP. Details on page 7 ►
New WHO statement on disclosure of clinical trial data calls for more transparency

The World Health Organization (WHO) has published a new statement on the public disclosure of clinical trial results, demanding greater transparency.

On 14 April 2015, WHO issued a public statement calling for the disclosure of results from clinical trials of medicinal products, whatever their findings. The move aims to ensure that decisions related to the safety and efficacy of vaccines, drugs and medical devices are supported by the best available evidence.

In an essay published in PLoS Medicine to coincide with the release of the position paper, a WHO author team describes the statement as a “[re-affirmation of] the ethical imperative of clinical trial results reporting” as well as an “[update and expansion of] WHO’s 2005 statement that ‘registration of all interventional trials is a scientific, ethical, and moral responsibility’”.

Dr Marie-Paule Kieny (WHO Assistant Director-General for Health Systems and Innovation) highlighted the importance of sharing scientific knowledge in order to advance public health, stating that, “It underpins the principal goal of medical research: to serve the betterment of humanity.” She went on to explain that, “Failure to publicly disclose trial results engenders misinformation, leading to skewed priorities for both R&D and public health interventions.”

Dr David Tovey, Editor in Chief of the Cochrane Library, welcomed the statement, saying, “The announcement by the WHO about making available all previous unpublished studies is a substantial step forward.” He also noted: “For Cochrane this means that our researchers will have access to more of the data they need, in order to inform decision making by consumers of health care, health professionals and policy makers more effectively.”

Under-reporting

WHO highlights two examples of under-reporting:

• one study of large clinical trials (more than 500 participants) registered on ClinicalTrials.gov found that 23% of trials had no results reported, accounting for nearly 300,000 participants

• among clinical trials of vaccines against five diseases registered on a variety of databases between 2006 and 2012, only 29% had been published in a peer-reviewed journal by the WHO recommended deadline of 24 months following study completion.

WHO’s call for disclosure includes older unreported clinical trials, the results of which may still have an important bearing on scientific research today.

WHO also reaffirms the need for all clinical trials to be registered on a WHO primary clinical trial registry so that they are accessible through the International Clinical Trials Registry Platform. This will ensure transparency about which clinical trials have been performed and will allow the verification of compliance with public disclosure requirements.

The WHO statement expands on a 2005 call for all clinical trials to be registered, and the subsequent establishment of the International Clinical Trials Registry Platform. The registry platform regularly imports trial records from ClinicalTrials.gov, the ISRCTN registry, the EU Clinical Trials Register, the Australia New Zealand Clinical Trial Registry, the Pan African Clinical Trial Registry and the clinical trial registries of China, India, Brazil, Republic of Korea, Cuba, Germany, Iran, Japan, Sri Lanka, The Netherlands and Thailand.

In Europe, the requirement to publicly disclose trial results is addressed in the new Clinical Trial Regulation due to come into effect no earlier than May 2016. This mandates the reporting of summary results for all clinical trials using a new portal and database, which are currently being developed by the European Medicines Agency.

HRA defines end of study information for trial subjects

The UK’s Health Research Authority (HRA) has issued a guidance document that describes the information to be provided to subjects at the end of a trial.

The new guidance (entitled ‘Information for Participants at the End of a Study’) came into effect in England on 1 April 2015 and applies to all studies that were ongoing at the time. It is aimed at those undertaking clinical trials and other interventional or diagnostic studies involving patients, and includes studies that are terminated early and where there is little likelihood of the findings being published. The guidance describes the design and content of the information that must be supplied to participants – and their legal representatives, consultees, close relatives or close friends (where applicable) – at the end of a study.

In the context of the guidance, “end of study” is defined as the end of the individual’s participation in a clinical trial or other interventional or diagnostic study. The guidance notes that end of study information should cover the following:

- what participants can expect to happen to them at the end of a study, including the arrangements in place for treatment when the study stops and any requirements for the ongoing monitoring of side-effects
- how those who have participated in the research can access the study results
- how those who would rather not see the findings can opt out of the process
- an acknowledgement of the contribution that the subject has made to research and the improvement of healthcare.

Very short interventional studies (eg. single-dose or single-visit studies) may not require a separate end of study information sheet if all the required information – including how and when participants can expect to access summary study results – was clearly stated in the original participant information sheet (PIS). However, if this level of detail was not included in the original PIS, it must be communicated to the participants at a later stage.

Information provided at the end of a study is not intended to replace information supplied to participants at the beginning of a study in the original PIS; it should supplement the PIS and provide further details as the study is coming to a close. Some information, such as how the study findings will be communicated to participants, may not be known in detail at the study outset, and so the end of study information sheet allows for more current information to be made available. In addition, the end of a study can often be an anxious period for participants; the guidance therefore aims to ensure that subjects are provided with clear information on the options available to them at the end of their period of study participation.

Copies of any end of study information sheets that have been provided to participants must be submitted to the research ethics committee, alongside the final report.

Source: <http://bit.ly/1b0f1vU>
CIRS finds improvements in regulatory efficiency

The Centre for Innovation in Regulatory Science (CIRS) has examined trends in the approval of new medicines by six regulatory agencies.

CIRS (formerly the CMR International Institute for Regulatory Science, <www.cirsci.org>) facilitates the development of regulatory policy across the international pharmaceutical industry, regulatory authorities and academia. It publishes regular R&D Briefings covering a broad range of regulatory and related topics that are of interest to Advisor readers. In particular, R&D Briefing 55 (available via the link shown below) assesses the impact of the changing regulatory environment on the approval of new medicines by six regulators and compares metrics relating to their regulatory activities in 2013.

The drug development and regulatory environments have continued to evolve over recent years, driven by the need to get valuable new medicines to patients more quickly and efficiently. Regulators have contributed by reducing the time needed to approve new medicines. As part of its efforts to advance regulatory policy, CIRS monitors regulatory performance and has analysed trends in the approval of new medicines between 2004 and 2013 by the following agencies:

- European Medicines Agency (EMA)
- FDA
- Health Canada
- Pharmaceuticals and Medical Devices Agency (PMDA, Japan)
- Swissmedic
- Therapeutic Goods Administration (TGA, Australia).

In R&D Briefing 55, CIRS highlights several of the factors that impact regulatory review time, including the type of review process, the type of product and the therapeutic area. It notes that, overall, there was less variability in median approval times for new active substances (NASs) across the six agencies in 2013 compared with the beginning of the review period, and that the gap in median approval time between the fastest and the slowest agency fell from around 500 days in 2004 to 200 days in 2013.

The report acknowledges reductions in within-agency approval times and outlines some of the key process changes that have helped specific agencies to achieve this. However, the lack of common processes across agencies potentially contributes to inter-agency variation. The report estimates the relative efficiencies based on a cumulative percentage of approvals over a fixed period of time, and uses this to measure how each agency has changed over the 10-year period. As expected, the efficiency of all six agencies improved from the beginning to the end of the period; however, there were notable differences between the agencies and these are explored in the briefing.

Expeditied review

Using data from the briefing, Table 1 summarises the NAS approvals by each of the agencies in 2013, comparing approval times by the type of NAS, therapeutic area, type of review and designation.

The number of approvals by each of the six agencies in 2013 varied from 23 (Swissmedic) to 37 (Health Canada), while the median approval time ranged from 304 (FDA) to 511 days (Swissmedic). The benefits of an expedited review programme are evident, with Swissmedic in particular achieving much quicker approval times under its expedited than its standard review process. Similarly, designated orphan NASs were approved more quickly than non-orphan NASs by four of the five agencies offering orphan designation, with Swissmedic not approving any orphan medicines in 2013.

Interestingly, there was no consistent trend in approval times for biological compared with chemical NASs. Intuitively, it might be expected that simpler chemical NASs might be approved more quickly than complex biological products, but this was not the case for the EMA, Health Canada, PMDA or TGA. However, assuming that biosimilars have been included in the definition of biological NASs, it may...
be that the reduced approval time needed for such molecules – especially in regions like Europe where there is a designated biosimilars regulatory pathway – has reduced the median approval time for biological products as a whole. If that is the case, the impact of biosimilars is likely to increase over time.

Source: summarised with the permission of CIRS from R&D Briefing 55, <http://bit.ly/1F0M7oi>

Table 1. Overview of regulatory approvals in 2013.

<table>
<thead>
<tr>
<th>Type of NAS</th>
<th>Number of NASs/median approval time (days)</th>
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<tr>
<th>Type of therapeutic area</th>
<th>Number of NASs/median approval time (days)</th>
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<tr>
<th>Type of review</th>
<th>Number of NASs/median approval time (days)</th>
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<table>
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<tr>
<th>Designation</th>
<th>Number of NASs/median approval time (days)</th>
</tr>
</thead>
</table>

Overall: 30/478, 29/304, 37/350, 28/342, 23/511, 25/391

EMA, European Medicines Agency; NA, not applicable; NAS, new active substance; PMDA, Pharmaceuticals and Medical Devices Agency (Japan); TGA, Therapeutic Goods Administration (Australia).

**Good practice guides aim to prevent medication errors in the EU**

The European Medicines Agency (EMA) has released two draft good practice guides that aim to improve the reporting, evaluation and prevention of medication errors by regulatory authorities and the pharmaceutical industry.

Medication errors are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient. They are the most common preventable causes of undesired adverse events in medication practice and represent a major public health burden.

With the entry into force of the EU pharmacovigilance legislation in 2012, the reporting of all suspected adverse reactions resulting from medication errors became mandatory. Pharmaceutical companies and national regulatory agencies in EU Member States are obliged to enter these adverse events into the EudraVigilance database. The primary purpose of the two guides – released by the EMA on 14 April, on behalf of the EU Regulatory Network – is to support the industry and regulators in the implementation of these legal requirements.

**Recording and assessment**

The first guide provides guidance on how suspected adverse reactions that are caused by medication errors should be recorded, coded, reported and assessed. It also gives recommendations for marketing authorisation holders on how to report information on medication errors that have not

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**Table 1. Overview of regulatory approvals in 2013.**

<table>
<thead>
<tr>
<th>EMA</th>
<th>FDA</th>
<th>Health Canada</th>
<th>PMDA</th>
<th>Swissmedic</th>
<th>TGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/478</td>
<td>24/304</td>
<td>31/352</td>
<td>23/345</td>
<td>18/508</td>
<td>22/401</td>
</tr>
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<td>6/270</td>
<td>11/349</td>
<td>7/270</td>
<td>10/50</td>
<td>9/391</td>
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<td>17/483</td>
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<td>26/353</td>
<td>21/360</td>
<td>13/548</td>
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<tr>
<td>27/481</td>
<td>18/364</td>
<td>28/355</td>
<td>17/306</td>
<td>19/579</td>
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</tr>
<tr>
<td>4/427</td>
<td>10/302</td>
<td>NA</td>
<td>8/252</td>
<td>0</td>
<td>7/362</td>
</tr>
<tr>
<td>26/481</td>
<td>19/338</td>
<td>NA</td>
<td>20/360</td>
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**Source:** summarised with the permission of CIRS from R&D Briefing 55, <http://bit.ly/1F0M7oi>
caused adverse reactions. Such information must be provided in the periodic safety update reports and risk management plans that are compulsory for all medicines. This allows regulators to make a continuous evaluation of the benefits and risks of a medicine, based on real-life data.

**Risk minimisation**
The second guide focuses on the prevention of medication errors. It describes the main sources and types of these errors and proposes measures to minimise the risk of medication errors throughout the lifecycle of a medicine. It includes a short section describing typical errors that may occur during a clinical trial programme.

While clinical trials may not reflect real-world use of a medication, the guide notes that medication errors are not uncommon in these settings. A study of oncology trials suggests that the most common types of errors relate to prescribing (66%), improper dose (42%) and omission errors (9%), with failure to follow an institutional procedure or the protocol the primary cause (39%), followed by failure to follow the written order (30%), and poor communication involving both the healthcare team and the patient (26%).

Common sources of medication errors in trials include the use of small font sizes and the absence of information on dose/strength in the plain packaging used for investigational products. Although such factors are unlikely to have an impact on the subsequent marketed product’s design or presentation, the clinical trial setting may help to identify any difficulties, particularly for medicines presented with a device or as a premixed solution for administration. Trial findings may also suggest refinements needed to the design of the product or to the instructions for use, prior to labelling, approval and marketing.

During clinical trials, it may become evident that certain drug product design features increase the risk of medication errors. In such cases, applicants should provide an appropriate risk analysis for medication errors detected in the clinical trial programme, and use this as a basis for refinement in the proposed pharmacovigilance and risk minimisation activities.

The delivery of the new guidance documents is one of the key deliverables of the EMA/Heads of Medicines Agencies joint action plan on medication errors agreed in 2013. It was developed in consultation with the European Commission’s Patient Safety Quality of Care Working Group, and takes into account the recommendations from stakeholders that were gathered during a workshop held at the EMA in February 2013.

Stakeholders’ comments on the two guides are invited by 14 June 2015.

**GCP lessons**

**Subjects receive incorrect trial drugs**

An FDA warning letter has highlighted how a busy trial site mixed up study drugs and gave the wrong medication to several subjects. The warning letter described several investigational drug dispensing errors, including the following:

- one subject was due to receive an unscheduled replacement investigational drug (a pen device); however, the study coordinator had also requested a replacement pen for another trial participant and inadvertently gave this pen to the subject
- on another occasion, a subject in one trial received and used the investigational drug pen that had previously been assigned to a subject in a different trial being performed at the same site.

The investigator acknowledged that these two subjects received the wrong investigational medicinal product (IMP) and indicated that he and his staff took full responsibility for the errors. He explained that he had since implemented new methods to prevent a recurrence of this type of violation, with two study coordinators now required to verify any medication assigned to trial subjects. The FDA accepted that, if properly carried out, this corrective action would be adequate to prevent similar violations in the future.

**Poor drug accountability**

However, IMP dispensing errors were not the only issue. The same site was found to have deviated from the approved safety procedures in five protocols and failed to implement proper drug accountability procedures.

Specifically, the protocols stated that randomised subjects with persistent hyperglycaemia (as defined in the protocol) should have either an adjustment of the dose of their trial drug or should receive hyperglycaemia rescue medication. Where subjects qualified for rescue medication, they were to attend the trial site for a rescue visit, which included efficacy and laboratory assessments.

In one of the trials, subjects were required to return trial medication dispensed at their prior visits when returning for titration/rescue visits, and they were to be instructed to take their new medication at the next scheduled dosing time. However, for one subject who qualified for a dose adjustment and received an increased dose of IMP, the inspection found that not all the unused medication was collected, and the subject was given the incorrect dose of trial medication at the titration visit.

The investigator claimed that the failure to collect all unused medication from this subject was the study coordinator’s mistake, and happened because the coordinator was handling a large number of investigational drugs for multiple clinical trials at the site. The investigator also indicated that the subject had been instructed to return the old pens to the trial site when attending the titration visit but had apparently not done so, and this led to the inadvertent use of an old pen instead of the more recently dispensed pen.

The same corrective action as noted above was proposed by the investigator (ie. for two study coordinators to verify any medication assigned to subjects). Although the FDA said that this was adequate if implemented correctly, the warning letter also stated that the investigator’s rationale for how the violation occurred was inadequate. It went on to highlight that it is the responsibility of the investigator, not the subject, to ensure that each trial subject receives the correct IMP.

**Lessons learned**

Given that Phase III clinical trials involving IMPs are typically undertaken to evaluate the safety, efficacy and tolerability of potential new medicines, it is crucial that enrolled subjects receive the medication that is assigned to them under the terms of the approved protocol and randomisation scheme, where relevant. Any deviations from the correct drug dispensing not only place trial subjects at risk but also undermine the value of the affected subjects’ trial data. Depending on the nature of the trial, this may have a significant impact on the overall trial database.

The requirements for drug dispensing and accountability are defined in GCP and also within the trial protocol. At the very least

- the date, subject number, number of doses and amount of drug dispensed to each subject should be recorded each time the trial drug is dispensed
- when a subject returns a trial drug, the amount used and unused should be documented, and an explanation provided for any inadvertent loss or destruction of supplies.

Although it was not mentioned in the warning letter, the trial monitor also has a role to play in maintaining complete drug accountability records. The monitor should verify that the IMP is being dispensed by the investigator or another authorised individual; in addition, during the trial the monitor should confirm that all supplies are accounted for and should investigate any discrepancies. By periodically reviewing drug accountability documentation during a trial, monitors can identify any deviations from the stated requirements and step in to ensure that staff are promptly re-trained where appropriate. Regular review of the IMP records can also help to identify other issues and ensure that corrective actions are implemented in a timely manner.

Source: <http://1.usa.gov/1sv4EBI>
New FDA guidance on changes to Risk Evaluation and Mitigation Strategy

The FDA has issued new guidance describing how it will define and process submissions from application holders for modifications and revisions to an approved Risk Evaluation and Mitigation Strategy (REMS).

The FDA Amendments Act of 2007 gave the agency the authority to require a REMS from manufacturers, to ensure that the benefits of a drug or biological product outweigh its risks. The REMS describes the elements that an application holder is required to implement to mitigate a specific serious risk listed in the labelling of a drug. All proposed materials included in the REMS (eg, communication and educational materials, medication guide, patient package insert) are approved and are appended to the REMS document.

The new guidance, issued on 6 April 2015, explains the types of REMS changes that will be considered to be modifications and those that will be considered as revisions. There are different procedures for the submission to the FDA of REMS modifications and revisions, as well as different timeframes for FDA review and action on such changes. The guidance therefore provides information on how these changes should be submitted to the FDA, and the agency’s process for review and subsequent actions.

Source: <http://1.usa.gov/1DGB70U>

UK confirms mandatory use of eCTD for decentralised procedures

The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) has issued a reminder that, from 1 July 2015, new marketing authorisation applications for decentralised procedures must be submitted in the electronic common technical document (eCTD) format.

Around 90% of new applications for decentralised procedures received by the MHRA are already submitted in the eCTD format and, moving forward, any marketing authorisation applications submitted in the non-eCTD electronic submission format will be rejected. Along with other national competent authorities, the MHRA intends to make this change mandatory in line with the EU roadmap.

New marketing authorisation applications for mutually recognised procedures will still be accepted in both non-eCTD electronic submission and eCTD formats. However, applicants are encouraged to use the eCTD format wherever possible, as use of the non-eCTD electronic submission format for these applications is planned to be phased out by 1 January 2017.