Agence Fédérale des Médicaments et Produits de Santé

DG PRE
Division research and development

YOUR LETTER FROM

YOUR REF.

OUR REF. FAGG/R&D/KFB

DATE

ANNEX /

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CIRCULAR NO. : 586
TO SPONSORS AND APPLICANTS FOR CLINICAL TRIALS

SUBJECT: **NATIONAL IMPLEMENTATION OF THE NEW VERSION OF THE "DETAILED GUIDANCE ON THE COLLECTION, VERIFICATION AND PRESENTATION OF ADVERSE EVENT/REACTION REPORTS ARISING FROM CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE ('CT-3')".**

THIS DOCUMENT IS A TRANSLATION OF THE OFFICIAL AND SIGNED VERSIONS IN DUTCH AND FRENCH.

Dear Madam, Dear Sir,

This circular replaces circular 460 and provides updated information on the notification of expected and unexpected serious adverse events when using an investigational medicinal product and on the submission of annual reports following the publication of the new version of the "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')" in the Official Journal of the European Union of 11 June 2011.

This document clarifies the changes implemented at the Belgian level by the FAMHP to put into practice the new version of the CT-3. This circular does not replace the CT-3 guideline in its entirety. Some aspects are clearly described in the CT-3 guideline and therefore do not require further explanation. Both documents (the CT-3 guideline and this circular) should be taken into account.

1. Scope

This circular is applicable to sponsors of interventional clinical trials with investigational medicinal products. An adverse event that occurs during an interventional clinical trial should only be notified or followed in accordance with the law of 7 May 2004 related to experiments on human people and with its implementation decrees.
Legislation related to pharmacovigilance for authorised medicinal products is not applicable here, even if authorized medicines are used. However, the reporting of adverse reactions occurring with medicinal products used in non-interventional clinical trials or in compassionate use programs or in medical needs programs follows the rules for authorised medicinal products. Among others we (would ask you to) refer to the current and future legislation on pharmacovigilance.

2. Definitions

Investigational Medicinal Product (IMP): an experimental medicinal product in accordance with the law of 7 May 2004 related to experiments on the human person.

Non-Investigational Medicinal Product (non-IMP, NIMP): a medicinal product that is used in a clinical trial but does not fall under the definition of an investigational medicinal product in accordance with the law of 7 May 2004 related to experiments on the human person.

Suspected Unexpected Serious Adverse Reaction (SUSAR): each suspected and unexpected serious adverse reaction related to an investigational medicinal product.

Reference Safety Information (RSI): the expectedness of an adverse event is determined using the Reference Safety Information. This should be done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product. Therefore, RSI may change during the conduct of a clinical trial. For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies. Consequently, a change in the RSI impacts on the number of adverse reactions to be reported as SUSARs.

3. Reporting of SUSARs

3.1. Reporting of SUSARs to the competent authority (FAMHP)

The sponsor of a clinical trial conducted in Belgium should notify all SUSARs (related to an IMP):

- Occurring in that clinical trial, irrespective of whether the SUSAR had occurred at a trial site in a Member State or at a trial site in a country outside the European Economic Area (EEA).

- related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in another Member State or exclusively in a country outside the EEA, if that clinical trial, is

    - sponsored by the same sponsor, or
    - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor.

The SUSARs should be sent in the ICH E2B format to the FAMHP through an *indirect reporting* through the EudraVigilance database (receiver ID: EVCTMPROD) of the EMA (European Medicines Agency). Additional questions relating to reporting through the EudraVigilance system can be sent to icsr@fagg-afmps.be .

Non-commercial sponsors who are not (yet) able to report electronically via the EudraVigilance database may request a provisional waiver establishing the procedures for reporting to the FAMHP.

3.2. Reporting of SUSARs to the Ethics Committee issuing the single opinion

The sponsor of a clinical trial conducted in Belgium should report all Belgian SUSARs occurring in clinical trial concerned to the Ethics Committee issuing the single opinion. A supplementary submission every 6 months of the list of all SUSARs is therefore not required.

The format for submission to the Ethics Committee issuing the single opinion is not defined. Electronic submission is possible but should be accepted in advance by the relevant Ethics Committee.

3.3. Informing the investigator

The sponsor should also inform all investigators. Information should be concise and practical. Therefore, this information should be aggregated in a line listing of SUSARs, accompanied by a concise summary of the evolving safety profile of the IMP. The sponsor determines the periodicity of this line listing as warranted by the nature of the clinical development project and the volume of SUSARs generated.

3.4. Unblinding

As a general rule only unblinded SUSARs should be reported to the FAMHP, as well as the Ethics Committee issuing the single opinion.

However, for trials in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another 'serious' outcome (that may potentially be reported as a SUSAR) is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, it can be defined during the approval of the dossier which serious events would be treated as disease- related and not subject to systematic unblinding and expedited reporting.

For such trials, sponsors are strongly encouraged to appoint an independent Data Safety Monitoring Board (DSMB) in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of the DSMB should be described in the protocol.

In all cases, following unblinding, if the event turns out to be a SUSAR, for example as regard expectedness, the reporting rules for SUSARs apply as described above.

4. Annual Safety Report – DSUR

The Annual Safety Report - ASR has developed into the DSUR format (Development Safety Update Report), in accordance with the ICH E2F "Note for Guidance on Development Safety Update Report (DSUR)" (EMEA/CHMP/ICH/309348/2008).

The "Reference Safety Information (RSI)"in effect at the start of the reporting period serves as RSI during the entire reporting period. Therefore, it is strongly recommended to align the update of the RSI for a clinical trial with the DSUR data-lock point. This prevents inconsistencies between expectedness of reporting SUSARs and the annual safety report. Each change in the RSI should be submitted as a substantial amendment to the FAMHP and the Ethics Committee issuing the single opinion.

For clinical trials whose duration is less than one year, the ASR does not need to be written. In this case, the "clinical trial report" as a part of the end of trial notification acts as an ASR. Nevertheless, it is recommended to submit an ASR when several short trials are conducted with the same IMP.

The annual safety report is submitted to the FAMHP and to the Ethics Committee issuing the single opinion from the first authorization of a clinical trial with the IMP by the FAMHP and throughout the whole period during which a clinical trial is ongoing in Belgium with this IMP, i.e. until the "Last patient last Visit" in Belgium, or until the "End of Trial" criteria as defined in the protocol are met.

The annual safety report is sent as an unprotected pdf file on CD-ROM, accompanied by a cover letter to the following address: Federal Agency for Medicines and Health Products, Research and Development Division Place Victor Horta 40/40, 1060 Brussels. If the submission of an ASR is no longer required in Belgium, the FAMHP should be informed by regular mail.

Further information on the Development Safety Update Report may be found in the "Questions and Answers" document developed by the Clinical Trials Facilitation Group (CTFG) and published on the website of the Heads of Medicines Agencies (HMA):http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2011_12_22_Q___A_DSUR.pdf

Thank you for noting the contents of this circular.

Sincerely yours,

Xavier De Cuyper
Chief Executive Officer