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ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC PUBLIC CONSULTATION PAPER

1 Introduction

The French academic clinical trials safety working group (REVISE: groupe de réflexion sur la vigilance et la sécurité des essais) was created in 2007 on behalf of the French Hospital Federation (**FHF**) and of the French Academic Sponsor Coordination (**CPI**) to face the implementation of the EU Clinical Trials Directive (2001/20/EC) among non-commercial sponsors. REVISE gathers more than 80% of the French University Hospitals' safety clinical trials departments and the majority of French non-commercial sponsors. This French academic working group includes over 40 stakeholders.

2 Key issue n°2 to be addressed: inconsistent implementation of the clinical trials directive

Consultation item n°6 & n°7 – Reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

2.1 Assessment of seriousness

The actual definition of seriousness given in the Directive is the following:

Article 2 (o) 'serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

The definition of seriousness in the directive is incomplete and inconsistent with the CIOMS VI group, Volume 9A, the ICH E2A and the FDA

PROPOSAL:

REVISE suggests to add the 6th seriousness criterion: important medical event with a clear definition.

2.2 Assessment of expectedness

The actual definition of expectedness given in the Directive is the following:

Article 2 (p) 'Unexpected adverse reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

As general guidance is provided, the correct reference document and the version to use for assessing expectedness of a serious reaction is not very clear and can finally impact on the risk benefit balance of clinical trials.

PROPOSAL:

REVISE suggests to have the possibility to use the Summary of Product Characteristics for authorised product which is being used outside the terms and conditions of the marketing authorisation that is mainly the case for non commercial sponsors

To change the version of the reference document only once a year (at the date of the first authorisation of the concerned clinical trial by a competent authority) or

To keep the same version of the reference document during the entire trial course to better assess the risk associated with clinical trials (a SUSAR will stay a SUSAR during all the study).

2.3 SUSAR reporting

REVISE suggests for SUSAR reporting in the future :

2.3.1 To National Competent Authority

- To report local SUSARs which occur within the concerned trial
- To report foreign SUSARs which occur within the concerned trial
- To report SUSARs which occur outside the concerned clinical trial

2.3.2 To Eudravigilance

- To report local SUSARs which occur within the concerned trial
- To report foreign SUSARs which occur within the concerned trial
- To report SUSARs which occur outside the concerned clinical trial

2.3.3 To Ethics Committees

In several Member States, the single opinion from Ethics Committee (article 7) is not implemented so reporting SUSARs appears difficult to comply with the different requests from Ethics Committees (different kind of SUSAR, different means of reporting, different timelines)

- To report local SUSARs **only** which occur within the concerned trial
- To grant a read-only access to Eudravigilance Database
- **Not** to report 6-month line listings

2.4 New safety issues

The new safety issues has to be reported to National Competent Authority and to Ethics Committees

2.5 Annual Safety Report (or Development Safety Update Report (DSUR) to be implemented soon)

The annual safety report has to be reported to National Competent Authority and to Ethics Committees

The actual definition of the annual safety report given in the Directive is the following:

Article 17 (2) Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

PROPOSAL:

REVISE suggests to report all serious adverse events and all serious adverse reactions that occurred during the trial not only during the one-year period covered by the report to have a global safety overview of the trial

When the DSUR will be implemented to keep the possibility to do :

An annual safety report for one trial which tested several Investigational Medicinal Products (mainly the case in non-commercial clinical trials

Or an annual safety report for several clinical trials conducted with the same Investigational Medicinal Product

2.6 Miscellaneous

In the future, for a better reporting from investigator to sponsor of serious adverse events occur in clinical trials,

(1) EMEA could create a mailing list of all investigators (data can be extracted from eudraCT) to send :

a reminder of all good clinical practices at the beginning of the trial

all safety alerts/issues during the course of the study

(2) EMEA could establish/diffuse for all investigators and sponsors, basic standard operating procedures with minimum requirements to ensure patient' safety

3 Conclusion

To adopt the text of the Clinical Trial Directive in a form of a regulation

To limit reporting to the Ethics Committees to local SUSARs/New safety issues/Annual Safety Report

To grant Eudravigilance access to the Ethics Committees