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Joint analysis

New Proposal for a Regulation on Clinical Trials:

- **The protection of human subjects must be upheld**
- **Citizens' right to information must be strengthened**

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New Proposal for a Regulation on Clinical Trials:
- The protection of human subjects must be upheld
- Citizens' right to information must be strengthened

**Introduction: Directive 2001 versus proposed new Regulation:
throwing out the baby with the bath water?**

The core piece of European legislation on clinical trials, Directive 2001/20/EC, adopted in 2001, is unanimously acknowledged to have “*brought about important improvements in the safety and ethical soundness of clinical trials in the EU and in the reliability of clinical trials data*” (1).

However, Directive 2001/20/EC has been accused of resulting in a costly administrative burden to multinational clinical trials due to differences in application dossier requirements across Member States (2).

In order to justify the need to revise the EU regulation on clinical trials, the European Commission claims that “*the number of applications for clinical trials fell by 25% from 2007 to 2011*” in the EU, while recognising that “*it would be wrong to attribute the fall in clinical trial activity solely and exclusively to the Directive 2001/20/EC*” (2). Indeed, the worldwide context must be taken into account (a).

On 17 July 2012, the European Commission presented its proposal for a new Regulation on clinical trials (2). It is aimed at “*fostering EU's attractiveness in clinical research*” and would repeal Directive 2001/20/EC (3).

On one hand, several measures of the proposed Regulation are welcomed, notably:

- **The establishment of a more harmonised application dossier** for the initial authorisation and substantial modification of clinical trials (*Annexes 1 and 2 of the proposed Regulation*);
- **The creation of a single and improved “EU portal” linked to an EU database** (*Articles 77 and 78 of the proposed Regulation*) to allow:
 - o Sponsors to submit an application to conduct a clinical trial at a single point,
 - o Member States to share work and information,
 - o The public to access certain information more easily.

However, it is not clear whether or not this “EU portal” — to be set up and maintained by the European Commission — would replace the EU database EudraCT, that is currently maintained by the European Medicines Agency (b).

- **The establishment of a national indemnification mechanism in all Member States**, in order to help “non-commercial sponsors” in particular to obtain coverage for possible compensation for any damage suffered by trial subjects (c) (*Chapter XII, Article 73 of the proposed Regulation*).

On the other hand, it seems that the European Commission has overlooked important improvements provided by Directive 2001/20/EC for the protection of subjects enrolled in clinical trials. Most remarkably, the proposed Regulation could seriously undermine Member States' subsidiarity on ethical matters.

a- For more than a decade, the pharmaceutical industry has faced a serious innovation crisis. The current corporate-based model for research and development is increasingly criticised and many academics and researchers are calling for independent clinical trials to test drugs (refs. 14,15).

Moreover, it is — and will remain — easier and cheaper for pharmaceutical companies to conduct clinical trials in large developing countries (China, India) where participant recruitment is more straightforward (ref. 13).

b- EudraCT, the database for all clinical trials initiated in the Community from 1 May 2004 onwards, was established in accordance with Directive 2001/20/EC. In November 2012, the European Medicines Agency (EMA) clearly expressed its commitment to providing public access to clinical trial data and called for a clear legal framework to support the implementation of transparency requirements (ref. 16).

c- According to the impact assessment, such coverage was difficult for “non-commercial sponsors” to obtain through insurance (ref. 2).

Deregulation under the guise of “simplification”

Several measures contained in the EU Commission’s proposed new Regulation on clinical trials are deregulation measures for interventional research in human subjects.

Dangerous change to the definition of a clinical trial. Directive 2001/20/EC (*Article 2(a)*) provides a comprehensive definition of a clinical trial, including “any interventional investigation in human subjects (...)” (d).

However the new proposed Regulation puts forward new, confusing definitions:

- it proposes renaming a “clinical trial” as defined by Directive 2001/20/EC as a “clinical study” (*Article 2(1) of the proposed Regulation*);
- it proposes narrowing the definition of a “clinical trial” to:
“a clinical study which fulfils any of the following conditions:
(a) the investigational medicinal products are not authorised;
(b) according to the protocol of the clinical study, the investigational medicinal products are not used in accordance with the terms of the marketing authorisation of the Member State concerned;
(c) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
(d) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
(e) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.” (*Article 2(2) of the proposed Regulation*).

In addition to defining studies by default as “non-interventional” (*Article 2(4) of the proposed Regulation*), **this new narrowed definition of a clinical trial would allow certain interventional clinical trials to be labelled as “clinical studies”, which would therefore fall outside the scope of the new Regulation on clinical trials.**

Such interventions in humans (i.e. trials with a previously authorised medicine in the framework of post-authorisation efficacy or safety studies or phase IV studies, when no additional diagnostic or monitoring procedures are required compared to normal clinical practice) could thus be conducted without having to ask for any authorisation from the Member States concerned or for the subjects’ informed consent! This is inconsistent with the Charter of Fundamental rights in the European Union (4). It would reopen the door to “seeding trials”, marketing studies used to push prescribers to “test” new drugs on their patients (5).

- ▶ **In order to prevent European citizens being used as guinea pigs without even being asked to give their consent, a simple principle should be applied: ‘observation’ could be included in the definition of a “study”, whereas ‘intervention’ should fall into the definition of a “trial”.**
- ▶ **The comprehensive definitions contained in Directive 2001/20/EC should be reintroduced:**
 - **renaming a “clinical study” as defined by *Article 2(1) of the proposed Regulation* as a “clinical trial”;**
 - **deleting the new narrowed definition of a clinical trial (*Article 2(2) of the proposed Regulation*);**
 - **replacing the definition of studies as “non-interventional” by default (*Article 2(4) of the proposed Regulation*) with the comprehensive definition of *Article 2(c) of Directive 2001/20/EC* (e).**

d- According to Article 2(a) of Directive 2001/20/EC, a clinical trial is defined as “any investigation in human subjects intended to:

- discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s),
- and/or to identify any adverse reactions to one or more investigational medicinal product(s)
- and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy” (ref. 1).

“Low-intervention clinical trials”: caution is needed. In an attempt to “better differentiate the obligations according to the risk-profile of the trial”, a new subcategory of clinical trial is defined.

A “low-intervention clinical trial” is defined as: “a clinical trial which fulfils all of the following conditions:

- (a) the investigational medicinal products are authorised;
- (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is a standard treatment in any of the Member States concerned;
- (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.” (Article 2(3) of the proposed Regulation).

When the investigational medicinal product is subject to a post-authorisation study, it is used in accordance with the terms of the marketing authorisation but can, nonetheless, still pose greater additional risks to subjects’ safety. Examples are the REGULATE study with *benfluorex* (Mediator^o) or the VIGOR study with *rofecoxib* (Vioxx^o) (f).

For “low-intervention” clinical trials, the sponsor does not have to “ensure that compensation in accordance with the applicable laws on liability of the sponsor (...) is provided” (Article 72 of the proposed Regulation). This means that participants in post-authorisation safety studies — which are being conducted because there are concerns about adverse drug reactions – would, paradoxically, have no right to compensation from the sponsor (g)!

- ▶ **The definition of a “low-intervention clinical trial” needs to be amended to exclude post-marketing efficacy studies and post-marketing safety studies. These should fall into the standard definition of a clinical trial** (amend Article 2(3) of the proposed Regulation);
- ▶ **No clinical trials should be excluded from national compensation mechanisms** (amend Article 72 of the proposed Regulation).

“Substantial modification”: wiggle room for scientific misconduct. According to Article 15 of the proposed Regulation, when modifications to an approved trial are “likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated” (‘substantial modification’ as defined in Article 2(12) of the proposed Regulation), they should be subject to an authorisation procedure similar to the initial approval. Yet, it is entirely up to the sponsor to decide whether a modification is substantial or not, despite its inherent conflict of interest.

Evidence shows that protocol changes are widely used to “torture the data until they confess” and represent one of the major hindrances faced by researchers trying to interpret trial outcomes (6).

- ▶ **Any protocol modifications should be dated and published on the EU portal so that they become part of the public record.**
- ▶ **The definition of a “substantial modification” should include the early termination of a clinical trial** (amend Article 2(12) of the proposed new Regulation) (h).

e- In order to prevent studies being conducted simply for marketing purposes (refs. 6,14), the following stipulation should be added to the definition of a non-interventional study: “No payment or other advantage can be provided to healthcare professionals in order to encourage them to prescribe, dispense or use a given medicinal product”.

f- *Benfluorex* (Mediator^o) and *rofecoxib* (Vioxx^o) were withdrawn from the market for safety reasons once the results of studies that would have come under the definition of a low-risk trial were made public:

- The REGULATE study with *benfluorex* (Mediator^o) exposed patients to the additional risk of developing heart valve disease (ref. 17);
- The VIGOR study with *rofecoxib* (Vioxx^o) exposed patients to more risk of cardiovascular adverse drug reactions than patients in normal clinical practice taking another, safer anti-inflammatory drug such as *ibuprofen* (refs. 18,19).

g- Participants would have to establish the producer’s liability according to Directive 85/374/EC (liability for defective product), which is very difficult.

h- Early termination is a common practice, especially when interim results show statistically significant results that are favourable to the trial drug. By halting the trial, sponsors avoid the risk of obtaining different results by the end of the trial if the statistically significant interim results were only due to chance. Moreover, early termination limits the trial’s ability to detect adverse drug reactions that develop after some time but may nevertheless be serious.

Member States' subsidiarity on ethics at risk of being seriously undermined

The proposed Regulation seems to suggest that the EU Commission considers the authorisation procedure for the conduct of a clinical trial as a simple administrative formality, overlooking the ethical issues that are at stake.

'Disappearance' of Ethics Committees. In order to ensure better protection for subjects enrolled in clinical trials in the EU, Directive 2001/20/EC's core measure was the establishment of Ethics Committees in all Member States. Ethics Committees have to *"give their opinion, before a clinical trial commences"* on the relevance and acceptability of the clinical trial (*Article 6 of Directive 2001/20/EC*). To do so, they have to assess the trial design, the protocol, and to evaluate the anticipated benefits and risks for the subjects: methodological and ethics assessments cannot be separated.

The proposed Regulation proposal **deletes all reference to Ethics Committees**, replacing it with a vague statement on the need for *"persons assessing the application"* to have no *conflicts of interest*ⁱ notably with respect to the clinical trial's sponsor (*Article 9 of the proposed Regulation*).

Moreover, **the roles of independent Ethics Committees and of Competent Authorities in Member States are no longer differentiated**, despite the conflict of interest of drug regulatory agencies when assessing trial applications for which they provided scientific advice (i) (2).

The deletion of all reference to Ethics Committees allows Member States and third countries to stop establishing independent Ethics Committees, notwithstanding the fact that internationally agreed standards have recognised independent Ethics Committees as an effective tool to ensure the protection of subjects enrolled in clinical trials.

In conjunction with other measures, such as untenable deadlines for the assessment of applications by Member States, automatic *"tacit authorisation"*, even on issues related to ethics, and the pared-down *"ethics assessment"* by Member States (read below), **the new proposed Regulation could seriously weaken the protection of subjects enrolled in clinical trials.**

Moreover, the shortened definition of a sponsor — which no longer includes financial responsibility (*Article 2(13) of the proposed Regulation*) — implies that those pharmaceutical companies that outsource clinical research to third parties (i.e. to contract research organisations or scientific societies) would no longer be defined as clinical trial sponsors, thereby exempting them from the sponsor's responsibilities. **If *"the rights, safety and well-being of the subjects shall prevail over the interests of science and society"* as claimed in Article 28 of the proposed Regulation, then:**

- ▶ **The internationally recognised ethical and scientific quality standards provided for in Directive 2001/20/EC, particularly the requirement for the establishment of Ethics Committees, should be upheld** (amend *Article 9* to reintroduce a clear role for independent Ethics Committees and to clarify the respective roles of Member States' Competent Authorities (i.e. the drug regulatory agencies) and Ethics Committees);
- ▶ **Explicit involvement of independent Ethics Committees in both Part I and Part II of the assessment should be required:**
 - **amending *Article 6 of the proposed Regulation* to reintroduce two criteria to guide Part I of the assessment: the acceptability of the trial and the significance of any benefit for the subjects involved;**

i- Companies involved in developing medicines sometimes pay drug regulatory agencies for scientific advice on the appropriate tests and studies to conduct, to maximize their chances of obtaining marketing authorisation.

The European Commission itself explains: *"The proposed Regulation does not 'mix' the aspect of scientific advice with that of a clinical trial authorisation [notably because] (...) it is perfectly conceivable (...) that these two approaches come to conflicting results: while, from the point of view of a future successful marketing authorisation, it may be desirable to obtain certain clinical data on the basis of experiments on humans, those clinical trials may not be acceptable from the point of view of subject protection."* (ref. 2 page 6).

- amending *Article 7 of the proposed Regulation* to add that subjects' protection should be taken into account;
- clearly stating that a negative decision by an Ethics Committee must preclude approval (see our proposed amendment to *Article 8(2) of the proposed Regulation* below on page 7);
- ▶ The definition of a sponsor should include *“an individual (...) or organisation which takes responsibility for (...) financing”* the trial (amend *Article 2(13) of the proposed Regulation*).

A single assessment for all Member States concerned, with very few possibilities to “opt-out”. In order to simplify the conduct of multinational clinical trials in the EU, Directive 2001/20/EC provided for a single opinion to be given per Member State (*Article 7 of Directive 2001/20/EC*). The new proposed Regulation aims at further centralisation: it **proposes a single assessment for all Member States concerned** (*Articles 5 to 8 of the proposed Regulation*).

To achieve this, the new proposed Regulation proposes an **assessment in two parts** that artificially disconnects the “scientific assessment” by the reporting Member State (Part I) (*Articles 5 and 6 of the proposed Regulation*) from a make-believe “ethics assessment” by Member States, which would be more or less limited to checking compliance with the requirements for informed consent (Part II) (*Article 7 of the proposed Regulation*).

Article 5(1) of the proposed Regulation states that the “sponsor shall propose one of the Member States concerned as reporting Member” with the risk that a sponsor systematically “cherry picks” a Member State that is more ‘flexible’ in its assessments than other Member States concerned.

Moreover, according to *Article 8(2) of the proposed Regulation*, **the reporting Member State’s assessment (Part I) is binding on other Member States concerned (j) except on two very limited grounds:**

- *“infringement of the national legislation referred to in Article 86 [Medicinal products containing, consisting of or derived from cells];*
- *significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice”; and only if the concerned Member State communicates its disagreement within 10 days to “the Commission, to all Member States, and to the sponsor” together “with a detailed justification based on scientific and socio-economic arguments”.*

In short, the rights of the Member States concerned to assess the acceptability of a clinical trial are reduced to the right to communicate any relevant “considerations” to the reporting Member State, and disagreement with the conclusions of the reporting Member State cannot be on the grounds of their own assessment of acceptability.

▶ **In order to uphold the rights of concerned Member States to effectively assess the acceptability of a clinical trial:**

- **the reporting Member State should be assisted by a co-reporting Member State in the assessment of applications** (amend *Article 5 of the proposed Regulation*);
- **the reporting Member State should be required to duly document and share any eventual disagreement by other Member States concerned** (amend *Article 6 of the proposed Regulation*);
- **at least two conditions enabling Member States to “opt-out” should be added to the list of grounds provided in *Article 8(2) of the proposed Regulation*:**
 - **NEW (c):** The existence of more comprehensive national provisions to protect subjects enrolled in a clinical trial, particularly with respect to vulnerable populations;
 - **NEW (d):** The refusal of the concerned independent ethics committee to approve the conduct of the trial.

j- According to *Article 8(2) of the proposed Regulation*, “Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.”

Untenable timelines and unacceptable “tacit authorisation”. Directive 2001/20/EC did not introduce the concept of tacit authorisation to conduct a clinical trial. Directive 2001/20/EC introduced the concept of tacit administrative authorisation so that a clinical trial could start provided the Ethics Committee has issued a favourable opinion and only if the competent authority of the Member State concerned has not objected (k).

The timelines in the new proposed Regulation are too short to assess applications properly and are untenable (l). Moreover, failure by Member States to meet deadlines would result in “tacit authorisation”.

For example, a clinical trial could be declared “low-intervention” by default (*Article 5 points 3 and 4 of the proposed Regulation*) despite the implications for the protection of trial subjects. “Tacit authorisation” would also apply on completion of the reporting Member State’s assessment (Part I), even in the event of disagreement, if the Member State concerned fails to meet the 10-day deadline for communicating its disagreement, which moreover can only be on two very limited grounds (see above) (*Article 8(4) of the proposed new Regulation*).

Part I of the assessment deals with issues related to ethics (compliance with Chapter V on the protection of subjects, relevance and acceptability of the clinical trial). **Such a “tacit authorisation” procedure therefore undermines Member States’ subsidiarity** and is contrary to internationally agreed standards of protection for research conducted in human subjects (m).

► **Whereas a “tacit authorisation” procedure might be acceptable for purely administrative purposes once the clinical trial has been approved by the Ethics Committee, it is absolutely unacceptable when ethics issues are at stake.**

Make-believe ethics assessments by Member States (Part II): more or less limited to informed consent and restricted to “own territory”. One internationally recognised, core ethical principle of medical research is that research in humans has to be acceptable in terms of the risks and burdens it imposes on trial subjects (4,7).

Article 7(1) of the proposed Regulation however limits the ethical assessment by Member States (Part II) to checking compliance with “*the requirements set out in Chapter V for informed consent*” and a few other requirements (n), while further restricting the assessment to a Member State’s “own territory”.

k- According to *Article 9(1) of Directive 2001/20/EC*, “*the sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance*”. *Recital 11 of Directive 2001/20/EC* confirms that a “tacit” administrative authorisation by the Member States’ competent authority [often the drug regulatory agencies] is only possible “*if there has been a vote in favour by the ethics committee*”.

l- Examples of such untenable timelines include:

- 6 days for the “proposed” reporting Member State to check whether the application is complete and whether it is indeed a “low-intervention” trial where claimed by the sponsor, and, if applicable, to find another Member State willing to be the reporting Member State; then, if additional information is requested from the sponsor, the reporting Member State is allowed only 3 extra days following receipt to check the additional information provided (*Article 5 points 3 and 4 of the proposed Regulation*);
- 10 to 30 days for the reporting Member State to produce its assessment report (Part I), including asking the other Member States concerned for comments; then, if additional explanations are requested from the sponsor, only 3 to 5 additional days following receipt to finalise the assessment report (*Article 6 points 4 and 6 of the proposed Regulation*);
- 10 days for Member States to produce their assessment reports on ethical aspects such as informed consent (Part II) (*Article 7 of the proposed Regulation*);
- 10 days for a Member State to “*communicate its disagreement [on the reporting Member States’ assessment on Part I], with a detailed justification based on scientific and socio-economic arguments*” (*Article 8 points 1 and 2 of the proposed Regulation*).

m- I.e. *Article 15 of the Declaration of Helsinki (2008)*, *Oviedo Convention on Human Rights and Biomedicine*, *Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH)*, etc.

n- In addition to compliance with “*the requirements set out in Chapter V for informed consent*”, *Article 7(1) of the proposed Regulation* states that Part II of the assessment should also address compliance with:

Limiting ethical assessment to checking the informed consent procedure undermines Member States' subsidiarity and responsibility towards their populations.

- ▶ **The proposed Regulation must take into account the diversity of the ethical assessment procedures of Member States for the protection of subjects enrolled in clinical trials, a principle that is respected by internationally recognised standards.**

A revision offering major opportunities to improve healthcare

The revision of the Clinical Trials Regulation offers two major opportunities to improve healthcare in Europe, by:

- requiring that new medicines be tested in comparative clinical trials against the “best current proven intervention”;
- improving citizens' access to information, including on safety issues.

Requiring comparative clinical trials. The Declaration of Helsinki (*Article 32*) specifies: “*The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention*” and warns against the use of placebo-controlled clinical trials stating that “*extreme care must be taken to avoid abuse of this option*” (7).

In fact, the use of placebo or an inappropriate comparator is unethical because it represents a loss of opportunity for clinical trials' subjects.

Moreover, a clinical trial that compares the new drug against the ‘best current proven intervention’ (the existing ‘gold-standard’ or ‘reference’ treatment) assesses the therapeutic advance that the new medicine represents. Such trials encourage real innovation to meet patients' needs, and avoid exposing EU citizens to new drugs that are actually less effective and/or more harmful than existing options (o).

- ▶ **The requirement for comparative clinical trials of new drugs against the ‘best current proven intervention’ should be added as a ‘General principle’** (amend the *beginning of Chapter 2 of the proposed Regulation*);
- ▶ **The term ‘best current proven intervention’,** defined as *‘the treatment regimen followed to treat, prevent, or diagnose a disease or a disorder according to current reliable scientific evidence’* (amend *Article 1(6) of the proposed Regulation*), **should replace the term “normal clinical practice” throughout the text.**

Improve citizens' access to information. Patients take part in clinical trials also in the hope that their participation will benefit the advancement of science (8). Yet many clinical trial results are never published, which diminishes the social value of research. Selective publication, especially when trial results are negative, is a common corporate practice that biases science and leads to costly, inefficient and even dangerous decisions (6). One example is the stockpiling of millions of doses of the neuraminidase inhibitor *oseltamivir* (Tamiflu^o) by EU governments in 2009, wasting billions of euros of taxpayers' money, despite the lack of evidence that Tamiflu^o is effective in preventing the complications of influenza (9).

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- the arrangements for rewarding or compensating investigators and subjects, and for recruitment of subjects;
 - protection of individuals with regard to the processing of personal data;
 - the suitability of individuals involved in conducting the clinical trial and the suitability of trial sites;
 - damage compensation;
 - the applicable rules for the collection, storage and future use of biological samples of the subject.

o- One well known example of such therapeutic regression is that of *rofecoxib* (Vioxx^o), an anti-inflammatory agent that was marketed even though it was no more effective than *ibuprofen*, but it exposed patients to more risks. In 2004, after having been marketed for several years, it was withdrawn when independent teams of scientists demonstrated an increased incidence of cardiovascular adverse reactions, many of which were fatal (notably myocardial infarction) (ref. 19). Another very recent example (January 2013) is that of *nicotinic acid + laropiprant* (Tredaptive^o, Pelzont^o and Trevaclyn^o): marketing authorisation was granted prematurely and the medicines were then withdrawn for safety reasons (ref. 20).

Public access to detailed and summary raw clinical data is particularly important to safeguard public health as it allows independent analysis. Any exceptions to disclosure should require detailed substantiation, should never apply to an entire document, and should only be granted on a temporary basis (6,9).

In order to reduce publication bias, Directive 2001/20/EC requires that the results of all trials be published within one year of their completion. However, studies in the US and in Europe show that about 70% of clinical trial results are not reported to the competent authorities within one year of the end of the clinical trial (10,11).

Unfortunately, the proposed Regulation does not include a clear provision on the right of the public to access clinical trial data. It only requires sponsors to “submit to the EU database a summary of the results of the clinical trial (...) within one year from the end of a clinical trial” (*Article 34 (3) of the proposed Regulation*), with no sanctions for non-compliance.

If public access to information is to become a reality and not merely wishful thinking, several measures should be implemented:

- ▶ **A Universal Trial Number (UTN)** (to be granted by the World Health Organization) (12) **or a registration number in the EU database, assigned to each clinical trial, should be mandatory before an application can be assessed** (to ensure that a clinical trial is duly registered and help track subsequent modifications);
- ▶ **Trial objectives should be specified:** regulatory/marketing purposes or non-commercial purposes, to be mentioned on informed consent forms (to increase transparency and better inform trial subjects);
- ▶ **The definition of a ‘protocol’ should include any subsequent versions of the initial protocol in the event of modifications** (amend *Article 2(20) of the proposed Regulation*);
- ▶ **The general principle of public access to information should be clearly stated**, for example in *Article 78 (2) on the objectives of the EU database*, **as should a commitment that “Regulation (EC) No 1049/2001 shall apply to documents held by the Agency”** (in order to increase the transparency of the European Medicines Agency);
- ▶ **In addition, to allow for effective implementation of the general principle of transparency:**
 - **the format for comprehensive access to raw clinical trial data should be specified** (add a new definition, that of the ‘clinical study report’, to *Article 2 of the proposed Regulation (p)*), **refer to these ‘clinical study reports’ in Article 34 of the proposed Regulation**, and **require that hyperlinks for easy access to these ‘clinical study reports’ be inserted in the Common Technical Document and in Public Assessment Reports** (amend *Articles 53 and 78(7) of the proposed Regulation*);
 - **a clear commitment should be made to make public the reporting Member State’s assessment report** (amend *Article 6(2) of the proposed Regulation*);
 - **in the event of non-compliance with the Regulation’s obligations, corrective measures taken by Member States and a summary of the outcomes of inspections by Member States or by the Commission should be made publicly available using the EU portal**, as the US Food and Drug Administration does on its website (amend *Articles 74, 75 and 76 of the proposed Regulation*);
- ▶ **Instead of archiving the clinical trial master file for just 5 years as proposed, it should be kept for a minimum of 30 years after the end of the clinical trial or, if the investigational medicinal product tested has been granted marketing authorisation based on the results of the clinical trial, throughout the marketing authorisation life of any of the active substances being investigated and/or any biosimilars or bioequivalents, plus an additional 30 years** (amend *Article 55 of the proposed Regulation*);
- ▶ **In order to foster compliance with the requirements of the proposed Regulation:**

p- The ICH E3 guideline defines a ‘Clinical study report’ as a report containing the full protocol and any subsequent modifications and dates thereof, a statistical analysis plan, summarised efficacy and safety data on all outcomes, and individual anonymised patient data in the form of tabulations or listings (ref. 9).

- **harmonised requirements should apply; for example any clinical data submitted as part of the Common Technical Document to obtain marketing authorisation must have been obtained from registered clinical trials that duly complied with the provisions of this Regulation** (addition to *Article 25 of the proposed Regulation*) (**q**); this requirement would discourage the conduct of unethical trials in third and developing countries (**r**) (13);
- **harmonised sanctions should be enforced by the Member States concerned, for example by refusing to approve any further applications to conduct new clinical trials submitted by sponsors that fail to comply with the requirement to publish the results of previously conducted clinical trials.**

Adverse drug reaction reporting: do not let the fox guard the henhouse. The proposed Regulation provides that investigators shall only report suspected serious adverse events to the sponsor of the clinical trial (*Article 37 of the proposed Regulation*). Then, the sponsor has to report only suspected unexpected serious adverse reactions to the Agency through an “electronic database”, to be set up by the Agency, “without delay” but no timeline is provided (*Articles 36 and 38 of the proposed Regulation*).

However, experience shows that sponsors often fail to report adverse drug reactions to health authorities. Being in a position of ‘judge and defendant’, they tend to:

- unduly assess reported suspected adverse reactions as being unrelated to their product, or
- withhold information for as long as possible (**s**).

Moreover, the use of the electronic database means in practice that adverse drug reactions are registered using codes that can strip them of all clinical significance (**t**).

All serious adverse events must be recorded, carefully studied, and registered in the electronic database by the investigator. In fact, evidence from recent drug disasters (i.e. *rimonabant* (Acompli^o) or *rosiglitazone* (Avandia^o)) indicates that they could have been avoided if due consideration had been given to the serious adverse events reported during clinical trials (**u**). Moreover, what is the justification for reporting only unexpected adverse events during clinical trials, when all suspected adverse events are to be reported once the product is authorised?

q- Clinical trials are often conducted in order to obtain marketing authorisation or a variation, for example to add new therapeutic indications. The real incentive to ensure compliance with the European legislation would be to prevent marketing authorisations from being based on data that come from unregistered clinical trials or trials which do not comply with this Regulation’s provisions.

r- It is easier for drug companies to conduct research in poor countries (informed consent regulations either do not exist or are weakly enforced). For example, Pfizer conducted a meningitis trial in Nigeria with its antibiotic *trovafloxacin* without parents knowing that their children were enrolled (ref. 21).

A recent response from the German government to parliamentary questions explains that it should not be possible to use unethical clinical trial data to obtain marketing authorisation for a medicine in Germany (ref. 22).

s- For example, during the summer of 2012, the withholding of pharmacovigilance data by two major pharmaceutical companies made the news:

- GSK agreed to plead guilty to criminal charges and to pay \$3 billion in fines, notably for failing to report safety data about its diabetes drug *rosiglitazone* (Avandia^o) (ref. 23);
- the European Medicines Agency started an infringement procedure to investigate Roche’s alleged non-compliance with pharmacovigilance obligations (ref. 24).

t- The way an event is coded can obscure what the event involved was. An enlightening example is that of antidepressants where suicides in children were coded as something else, e.g. ‘emotional lability’ or ‘hospitalisation’, in order to cover them up for as long as possible (ref. 25).

u- *Rimonabant* (Acompli^o) was licensed for the treatment of obesity. But one of its effects was that it increased the number of suicides. The European Medicines Agency’s response was initially confined to setting up a “risk management system” and it took about 2 years for it to be withdrawn from the market! The US Food and Drug Administration had refused to approve this drug from the outset on the basis that the risks detected in clinical trials were not adequately explained (ref. 26).

Despite the fact that their study was “limited by a lack of access to original source data”, independent researchers produced a meta-analysis of the available clinical trials with *rosiglitazone* (Avandia^o) and showed that “*rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance*” (ref. 27).

- ▶ In order to improve early detection of adverse drug reaction signals, the investigator — not the sponsor — should report all serious adverse events — whether unexpected or not — to the Agency or to the Member States concerned (via the electronic database), not just to the sponsor of the clinical trial. Reporting by investigators would:
 - avoid undue delays in decision-making, particularly when urgent measures are needed to protect subjects;
 - ensure that all serious adverse events are actually registered in the relevant EU databases (amend *Article 37 of the proposed Regulation*);
- ▶ Public access to the content of the “electronic database” should be provided (amend *Article 36 of the proposed Regulation*); moreover, the link between this “electronic database” and the existing EudraVigilance database should be clarified.

To conclude: several major improvements are needed

The EU Commission’s proposed new Regulation on clinical trials needs to be profoundly amended by the European Parliament and the Council, in order to:

- not undermine major improvements provided by Directive 2001/20/EC in the protection of human trial subjects;
- respect Member States’ responsibility to assess the acceptability of clinical trials;
- further improve the protection of trial subjects, and to foster real innovation that meets patients’ needs, by requiring comparative clinical trials of investigational products against the ‘best current proven intervention’;
- improve citizens’ access to information, including sensitive safety issues.

**Association Internationale de la Mutualité
(AIM)**

**Medicines in Europe Forum
(MiEF)**

**International Society of Drug Bulletins
(ISDB)**

Wemos

Cosignatory organisations



AIM. The Association Internationale de la Mutualité (AIM) is a grouping of autonomous health insurance and social protection bodies operating according to the principles of solidarity and non-profit-making orientation. Currently, AIM’s membership consists of 41 national federations representing 29 countries. In Europe, they provide social coverage against sickness and other risks to more than 150 million people. AIM strives via its network to make an active contribution to the preservation and improvement of access to health care for everyone. More info: www.aim-mutual.org. Contact: corinna.hartrampf@aim-mutual.org



MiEF. The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organizations representing the four key players on the health field, i.e. patients groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament of the importance of European medicines policy. Contact: pierrechirac@aol.com



ISDB. The International Society of Drug Bulletins (ISDB), founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org



Wemos. Wemos influences international policy in such a way that the right to health is respected, protected and promoted. In doing so, Wemos devotes special attention to vulnerable sections of society. Wemos advocates ethical conduct, coherent policy and equal access to care. Its lobbying work focuses on lasting improvements in Dutch, European and global policy. More information: www.wemos.nl. Contact: annelies.den.boer@wemos.nl

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