Paris, 15 June 2013
Response to a public consultation

Revision of the World Medical Association Helsinki Declaration:
- transparency of clinical trial results must be enhanced (articles 23, 24 & 26)
- caution is needed with the use of placebo (article 32)

Prescrire welcomes the opportunity to respond to the public consultation on the review of the Helsinki Declaration – Ethical principles for medical research involving human subjects (1).

Prescrire welcomes the proposed changes and would like to highlight particularly relevant elements of the draft revised text. When applicable, our suggestions for additional changes are visible in bold and underlined (additions) or stricken through (deletions).

The Helsinki Declaration as a stepping-stone

Since the Declaration of Helsinki enshrines universal ethical principles, it acts as stepping-stone to clinical research and as a guiding document in legislation and regulation. Therefore, article 2 of the Preamble, should bear that in mind:

> *"Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages other participants in medical research involving human subjects* ***as well as public institutions, authorities and regulatory agencies*** *to adopt these principles."*

First do no harm

Under the guiding principles contained in article 3, there should be a specific reference to the first do no harm principle, which is one of the principal precepts of medical ethics. This is particularly pertinent when taking into account the prevalence and burden of adverse drug reactions and the need to ensure patient safety.

> *"The declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patients' best interest when providing medical care.* ***The universal ethical principle of non-maleficence – Primum non nocere - should be the first consideration of a physician****."*

Evidence-based practice and the need for comparative trials

We welcome the changes to the declaration in what concerns Article 6. Clinical research should be guided and supported by evidence.

> *"Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality."*

Hence, the term best proven intervention is best suited to encompass the treatment regimen followed to treat, prevent, or diagnose a disease or a disorder according to current reliable scientific evidence.

Compensation from clinical research-induced harm

We fully support the inclusion of Article 15, which establishes that:

> *"Adequate compensation and treatment for subjects who are harmed as a result of participating in the research must be ensured."*

At present, compensation mechanisms are the exception rather than the rule. Participants accept to enter a trial to benefit science, but end up being penalized. Adequate compensation and treatment for participants who are harmed as a result of clinical research must be ensured.

Information about compensation mechanisms should be proactively included/delivered during the informed consent procedure (this aspect should also be held into account when reviewing in article 26 on informed consent).

[1] - World Medical Association. Declaration of Helsinki – Ethical principles for medical research involving human subjects. Draft revised text for public consultation, 15 April 2013. Available at: http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_plain.pdf: 5 pages.

Weighing risks of harm, burdens and benefits

Article 17 establishes the need to minimize risks and to monitor those throughout the trial.
We would like to point out that it is essential also to ensure the follow-up of harms incurring from the clinical research, once the trials are over. Trial participants must be followed-up by the lead investigators, and long-term adverse events from clinical research should be duly monitored and made publicly accessible. During the informed consent procedure trial participants should receive information on the risks of harm, but also on what to do and whom to contact should adverse drug reactions arise once the trial is terminated.

We propose the following addition to article 17 (in bold & underlined):

> *"Measures to minimise **harm** must be implemented. The risks must always be monitored by the researcher throughout **and after** the trial. **Trial participants should receive information on how to handle adverse events after the trial termination.**"*

Preventing misconduct

In order to prevent misconduct in clinical research, we welcome the changes to Article 22 and 23, whereby:
- the research protocol should discuss and justify the chosen study design;
- any changes to protocol must be duly justified and subject to authorisation by ethics committee.

We would strongly encourage:

- In addition to the publication of the summary, to make available on the Internet the full clinical study report (or raw data where a clinical study report is not available), within one year of the end or early termination of the trial and in a user-friendly and searchable format.
- that ALL adverse reactions be monitored by investigators and reported to ethics committees, not just serious adverse reactions.

We propose the following change to Article 23 (in bold & underlined):

> *"The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about **all** adverse events. At the end of the study, the investigators must submit a final report to the committee containing a summary of the study's findings and conclusions. **The investigators should also make publicly available the clinical study report, to enable public scrutiny and scientific replication. Sanctions should be applied if requirements are not met."***

Caution needed: privacy and confidentiality are increasingly used to avoid clinical data disclosure

As stated in article 24:

> *"Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information (…)."*

However, privacy and confidentiality should not be used as pretexts to hinder the disclosure of relevant clinical data. It is the responsibility of clinical trial investigators to protect their patients' personal data. By principle, disclosure should be the rule and not the exception.
What would volunteers who participate in clinical trials favour: that their contribution would allow early detection of a safety signal, preventing others from experiencing the same adverse effects? Or to see their data withheld?

Proportionality in ethics has to be taken into account. Even if some researchers, digging into the details of the clinical data, might in an exceptional case be able to identify a single patient (rare diseases), for what purpose would the researcher use that information? This "unlikely to happen" risk needs to be evaluated against the current situation, where millions of otherwise avoidable adverse drug reactions are taking place and where drug-induced harm is being routinely hidden.

We propose therefore the following change to Article 24 (in bold & underlined):

> *"Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information **but such precaution shall not hinder the publication of detailed anonymised clinical trial data. Every precaution must also be taken** to minimize the impact of the study on their physical, mental and social integrity."*

Informed consent procedures

On what concerns the articles relating to informed consent procedures:

- The trial identification number, information on where to find the trial results once the trial is terminated, as well as information about compensation mechanisms should also be proactively included and delivered to participants during the informed consent procedure. Additionally, trial participants should be informed, whether the clinical trial will be used to support a marketing authorisation application or for academic research.

We therefore propose the following change to Article 26 (in bold & underlined):

> *"In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, anticipated benefits and potential risks of the study and the discomfort it may entail, post trial access,* ***information about compensation mechanisms*** *and any other relevant aspects of the study.* ***The physician must also provide the identification number of the trial as well as additional information on the format, expected calendar date and platform for the public disclosure of the clinical trials results. Additionally, trial participants should be informed, whether the clinical trial will be used to support a marketing authorisation application or for academic (non-commercial) research".***

The physician must fully inform the patient which aspects of the care are related to the research, but also alert to potential care that might arise once the trial has ended, should adverse events occur.

We therefore propose the following change to Article 31 (in bold & underlined):

> *"The physician must fully inform the patient about aspects of the care that are related to the research* ***and also alert to potential care that might arise once the trial has ended, should adverse events occur. "***

The use of placebo

The current Declaration of Helsinki 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*" (1).

We support the use of the wording "*best current proven intervention*" which refers to evidence-based medicine. It prevents "discount" clinical trials being conducted in poor countries using a standard treatment that is not as effective and safe as the best proven intervention.

The use of placebo or of an inappropriate comparator is unethical because it represents a loss of (treatment) opportunity to participants. Moreover, healthcare professionals and patients are then unable to compare the new drug with existing treatments for the same indication.

Article 32 deals with an ethical principle and should not be undermined by a long list of exemptions.

The current situation is unacceptable: medicines tested in placebo-controlled trials are still being authorised into the market, even when effective and safe proven interventions already exist[2].

We therefore request further restricting the use of placebo, i.e. only where no current proven intervention exists:

> *"The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention(s) except in the following circumstances:*
> *The use of placebo, or no intervention is acceptable in studies where no current proven intervention exists";* ~~*or*~~
> ~~*Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, placebo or no treatment is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo or no treatment will not be subject to any additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.*~~ *Extreme care must be taken to avoid abuse of this option."*

Post-approval efficacy and post-approval safety studies are increasingly required since marketing authorisations are increasingly granted based on insufficient evidence. Nevertheless, post-approval efficacy and safety studies should also be conducted versus the best proven intervention in order to avoid a loss of (treatment) opportunity to participants.

Post-trial access to care

We welcome article 34, but would add the following changes (in bold):

> *"In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access**, monitoring and treatment of (long-term) adverse events** for all participants who still need an intervention identified as beneficial in the study. This information should also be disclosed to participants during the informed consent process. All study participants should be informed about the outcome of the study."*

The Helsinki Declaration as a tool to ensure transparency in clinical trials: Trial registration, publication of results and the role of lead investigators

Patients take part in clinical trials in the hope that their participation will benefit the advancement of science, improve healthcare, and ultimately benefit society at large ([3]). Clinical trial data are therefore scientific data and represent a public good.

While the Helsinki Declaration requires authors to make the results of their research on human subjects publicly available, many clinical trial results are never published, which greatly diminishes the social value of research. 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 ([4, 5]).
Moreover, by claiming ownership of clinical trial results, pharmaceutical companies are arguing for the right to keep secret information that could save lives and also advance biomedical research (e.g. making available data of earlier trials could avoid the repetition of similar trials, reducing both private and public expenditure). Selective publication, especially when trial results are negative, is a common practice that biases science and leads to costly, inefficient and even dangerous decisions ([6]).

The European Ombudsman has ruled that clinical study reports (CSRs) contain no "commercially confidential" information.

We fully support article 35 which requires every clinical trial to be registered in a publicly accessible database before recruitment of the first subject, as well as article 36 which establishes that researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication of the results of research.
Sharing detailed results of clinical research is an ethical obligation since it allows scientific and public scrutiny. Access to raw data may render a planned study superfluous, so it would be unethical not to provide access to raw data, as superfluous studies are by definition unethical.

We strongly encourage the inclusion of specific requirements into article 36, such as:

- the publication of all results (in clinical study report format) within one year of completion or early termination of the trial; and
- the requirement to make raw data available.

  *"~~Researchers,~~ **Investigators,** sponsors, editors and publishers have ethical obligations with regard to the publication of the results of the research. **Investigators** have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. **Trial results should be published in clinical study report format within one year of completion or early termination of the trial, and anonymised raw data shall be made available.**"*

Unproven interventions

We agree with the changes proposed clarifying that off-label use should "***subsequently*** *be made the object of research*" particularly since off-label interventions can be detrimental to patients' safety.

Prescrire

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References:

1- World Medical Association "Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects" (October 2008) Available at: http://www.wma.net/en/30publications/10policies/b3/.
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2- European Medicines Agency: reliance on placebo studies is unacceptable"Prescrire Int 2011; 20 (121): 278.

3- Kmietowicz Z "Trial participants call for drug regulator to ensure study results are published" *BMJ 2013;346:f382*.

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6- Gøtzche PC "Deficiencies in proposed new EU regulation of clinical trials" *BMJ* 2012; 345:e8522.