

**Opinion No 51 of 12 March 2012  
on the publication of the results of  
human experimentation**

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## ANNEXES 1 TO 4 OF OPINION: SEE SEPARATE DOCUMENT

# REQUEST FOR AN OPINION

On 15 October 2008, Dr. G. Bauherz, President of the Medical Ethics Committee of the Hospitals Iris Sud (HIS, Brussels), submitted the following question to the Advisory Committee on Bioethics (extract from his letter):

“When clinical studies are submitted, the HIS Ethics Committee regularly discusses the issue of the publication of findings.

In particular as regards studies on therapeutic medicinal products or techniques, we are unaware of what happens to the findings of studies that prove to be negative.

We would like to know whether the Advisory Committee has formulated an opinion on this subject and if not, we would like to be able to discuss it with you.”

At the plenary meeting of 17 November 2008, the question was declared admissible and allocated to the 'clinical research' select committee. The author of the question was informed of this in a letter of 19 January 2009. The Committee's third term of office ended on 20 April 2009 and the question was passed on to the fourth term, which partly explains the length of time taken to compile this opinion.

The 'clinical research' select committee reformulated the problem as follows:

When examining a protocol relating to human experimentation, can/must a medical ethics committee (MEC) check how the findings of the research – whether positive, negative or inconclusive – will be published or made publicly available?

There first of all follows an introductory consideration of the concept of 'clinical trial' in this opinion. The question, the context and the recommendations are then summarised.

The context is set out in points 1 and 2. Point 1 outlines the problem of the underreporting of research findings. The need for the prior or prospective registration of clinical trials and the publication of their findings is thus dealt with. The potential role of medical ethics committees is covered in point 2. Point 3 ends by presenting the general point of view and the recommendations of the Advisory Committee on Bioethics.

A few annexes then follow, providing additional information.

# INTRODUCTORY CONSIDERATION

First of all, the concepts that will be used throughout this opinion should be specified. The definition of clinical trials can, in fact, differ depending on the body or organisation concerned.

In European Directive 2001/20/EC relating to the implementation of good clinical practices in the conduct of clinical trials on medicinal products for human use, the definition adopted is somewhat narrow: clinical trials are understood to refer only to interventional studies concerning medicinal products (tested on humans). When transposing the European directive in the act of 7 May 2004 on human experimentation, the Belgian legislator took the definition of clinical trial as formulated in the directive (Article 2, 7<sup>o</sup>):

“clinical trial: any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmaco-dynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational medicinal products and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining its (their) safety and/or efficacy”.

However, the scope of application of the Belgian act covers far more than simply interventional studies with medicinal products, as can be seen from the following definition of the concept of 'experimentation' in Article 2, 11:

“Experimentation: trial, study or investigation in human subjects intended to develop knowledge specific to the exercising of health-care professions as referred to by Royal Decree No 78 of 10 November 1967 on the exercising of health-care professions.”

The act provides for an exception to Article 3, §2<sup>1</sup>: purely retrospective studies do not fall within the scope of application of the act.

It will be seen later in the opinion that the Dutch legislator has also introduced broader regulation of medical-scientific research than that provided for in the European directive. The *Food and Drug Administration* (FDA) in the United States also adopts a broader definition of a clinical trial than that formulated in the European directive. The Council of Europe and the World Health Organisation go even further in this definition.

In the following text, the term 'clinical trials' should be interpreted in the broad sense, that is in the sense of research carried out on humans, which also corresponds more closely to the scope of application of Belgian law, that is experiments conducted on human subjects that contribute towards the development of knowledge specific to the exercising of health-care professions. When reference is made to European Directive 2001/20/EC, this therefore refers only to interventional studies concerning medicinal products (see also the aforementioned definition of a clinical trial in Belgian law).<sup>2</sup>

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<sup>1</sup> Art. 3, §2: “This law does not apply to purely retrospective studies based on past data which are found in patients’ dossiers, medical dossiers or administrative dossiers or databases provided that under no circumstances are new data relating to these patients found.”

<sup>2</sup> In the introductory report for opinion No 13 of 9 July on human experimentation, the Committee defines the concept of experimentation in point B. It also explains the various phases of biomedical experimentation relating to substances that may be medicinal products, which corresponds to an interventional study concerning medicinal products in this opinion.

See web page:

[www.health.belgium.be/eportal/Healthcare/Consultativebodies/Commitees/Bioethics/Opinions/index.htm?&fodnlang=fr](http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Commitees/Bioethics/Opinions/index.htm?&fodnlang=fr)

# SUMMARY

Dr G. Bauherz, Chairman of the Medical Ethics Committee of the IRIS Sud hospitals (HIS, Brussels), put the problem to the Advisory Committee on Bioethics that the members of the medical ethics committee often do not know what happens to the findings of studies concerning therapeutic medicinal products or techniques that prove to be negative.

The Advisory Committee on Bioethics **reformulated** this request for an opinion as follows: When examining a protocol relating to human experimentation, can/must a medical ethics committee (MEC) check the way in which the findings of the research – whether positive, negative or inconclusive – will be published or made publicly available?

The opinion takes as a basis the **context** of the problem of the underreporting of research result (publication bias).

Several initiatives have been developed in the past decade that aim to promote the transparency and, consequently, the integrity of scientific research, including initiatives focusing on the mandatory prospective registration of clinical trials in public registers and guidelines on the publication of research findings.

The Council of Europe Guide (2010) intended for members of research ethics committees recommends that once their research is finished, researchers should (1) submit a report or a synopsis of their conclusions to the committee that initially assessed the research, and also (2) confirm their initial proposals regarding the publication of the findings in scientific journals or their public communication by other means. In order to thwart the publication of biased research findings, the Council of Europe guide also suggests making ethical approval by ethics committees subject to prospective registration of the protocol in a register that is accessible to the public. These committees should also always ask for all the findings of the research to be made public.

As a concrete example, reference can be made to the ‘Research contract assessment’ directive (*Richtlijn ‘Beoordeling onderzoekscontract’*) in which the Central Dutch Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek, CCMO*) entrusts to medical-ethical assessment committees (METC) the task of verifying whether the protocols do not contain any unreasonable restrictions with regard to the publication of research findings.

Starting from the **general point of view** that it is a matter of ethical duty to publish, as far as is possible, all findings – whether they are positive, negative or inconclusive – of scientific research carried out on humans, the Advisory Committee on Bioethics makes the following **recommendations** to the Belgian authorities.

- a. Medical ethics committees must be given the resources to fulfil their missions correctly.
- b. Medical ethics committees must be given the mission (1) to assess protocols in the light of the policy on the publication of the research findings and (2) to follow up protocols for which they have issued a positive opinion until the findings are published.
- c. The issue of the publication of all the findings of research must be tackled at European level, for example in the context of the revision of European Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

# 1. Registration and publication

In its opinion No 13<sup>3</sup>, the Advisory Committee on Bioethics considered the ethical problem raised by human experimentation.

The issue tackled here is the need for the prospective registration of all clinical trials<sup>4</sup> carried out on human subjects and the widest possible publication of their findings in order to prevent the underreporting of scientific discoveries. This relates to the problem of publication bias.

## 1.1. Underreporting of research findings

Research findings may or may not be statistically significant. The classification of findings as positive or negative, favourable or unfavourable, important or of no interest in itself involves interpretation.<sup>5</sup> Findings will usually be considered to be positive when they confirm the research assumption set out before the clinical trial: a new medicinal product put to trial, for example, is statistically more significant than the comparator (placebo or standard treatment).<sup>6</sup> Whatever the result, whether it is statistically significant or not, the extent of any differences found should also be examined.

When the classification of statistically significant or insignificant findings as 'positive', 'negative' or 'of no interest' influences their dissemination, underreporting or a publication bias regarding findings may occur. For instance, when positive findings concerning the efficacy of a new medicinal product are disseminated more widely than findings that are less positive or of no interest, this may give rise to an overvaluation of the efficacy of this medicinal product.<sup>7</sup>

### *NIHR 2010 report*

In the context of its *Health Technology Assessment Programme*, in February 2010 the *National Institute for Health Research* (United Kingdom) published a study report entitled "*Dissemination and publication of research findings: an updated review of related biases*".

As the title indicates, this report is an update of an initial report<sup>8</sup> published in July 2000 which concluded in particular that despite the uncertainty surrounding the extent, the orientation and the impact of publication bias, it seems reasonable to conclude that studies

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3 Opinion No 13:

[www.health.belgium.be/eportal/Healthcare/Consultativebodies/Comitees/Bioethics/Opinions/index.htm?&fodnlang=fr](http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Comitees/Bioethics/Opinions/index.htm?&fodnlang=fr)

4 Broad definition of clinical trial, see also preliminary consideration.

5 Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. (2010), "Dissemination and publication of research findings: an updated review of related biases". *Health Technol Assess*, 14(8), 234 p., p. 2.

For the report, hereinafter abbreviated to 'NIHR report 2010', see web page: [www.hta.ac.uk/project/1627.asp](http://www.hta.ac.uk/project/1627.asp).

6 Rasmussen N, Lee K, Bero L. (2009), "Association of trial registration with the results and conclusions of published trials of new oncology drugs", *Trials*, 10:116, see p. 4.

See web page: [www.trialsjournal.com/content/10/1/116](http://www.trialsjournal.com/content/10/1/116).

7 NIHR report 2010, p. 2.

8 Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. (2000), "Publication and related biases", *Health Technol Assess*, 4(10), 115 p.

For the full report, see web page <http://www.hta.ac.uk/project/1051.asp>.

which produce conclusive or positive findings are disseminated more and more quickly<sup>9</sup> than studies whose findings are inconclusive or negative.<sup>10</sup>

The 2010 update reaches a similar conclusion<sup>11</sup>, i.e. that the dissemination of research findings is a biased process the real impact of which is unknown. This should be taken into account when taking evidence-based decisions. This updated version makes reference to recent initiatives to promote the prospective registration of clinical trials and guidelines on the reporting of research findings, while stressing that the prospective registration of basic research, the early phases<sup>12</sup> of clinical trials and observations has not yet been sufficiently developed. Prospective registration only helps reduce publication bias when the findings of the studies registered are also accessible. For systematic reviews, the proposal is to systematically examine the studies published and not published in order to reduce the impact of publication bias.

*Examples of studies of the phenomenon of underreporting and related problems giving rise to biased information in medical-scientific literature.*

In a study by Turner et al.<sup>13</sup>, the reports from the American Food and Drug Administration (FDA) on clinical trials registered with the FDA concerning twelve antidepressants were compared with the findings that had been published in scientific reviews. Of the 74 clinical trials registered – in which a total of 12,564 patients had participated – nothing was published in 31 % of cases (~3.449 trial subjects). Virtually all the studies published (94 %) yielded positive findings whereas, on the basis of all the reports from the FDA – that is both published and unpublished data – only half (51 %) were positive. Of the 36 studies that produced negative or doubtful findings, 22 were not published. Of the 14 studies actually published, the findings were wrongly presented as positive in 11 cases. This study therefore noted not only the underreporting of research findings with a publication bias in favour of clinical trials with positive findings, but also a distortion of the findings themselves: study data with negative findings were presented in the publications in such a way that the findings seemed positive.

Another example referred to in an article by McGauran et al.<sup>14</sup> concerns a study of 900 clinical trials relating to 90 new medicinal products approved by the American FDA. The findings of just 43 % of the clinical trials were published. Moreover, selective reporting of the findings was observed in the publications: negative findings were presented in a positive fashion, the conclusions did not appear to be backed up by the findings, the side effects

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9 The broader concept of 'diffusion' or 'dissemination' is used in the NIHR report, to the extent that publication in a scientific review is only one of the possible ways of disseminating research findings, see NIHR report 2010, p. 2.

See also Rennie D. (2008), "The obligation to publish and disseminate results", in *The Oxford textbook of clinical research ethics*, Ezekiel J.E. et al., Oxford University Press, pp. 795-807, see p. 796.

10 NIHR report 2010, p. 1.

11 NIHR report 2010, pp. III and XI.

12 NIHR report 2010, p. 83: "Efforts so far have focused on the registration, publication and disclosure of confirmatory phase III/IV trials due to the perceived immediate consequences". This does not, however, mean that for subsequent phases of clinical trials, there is no longer any distortion of research results.

13 Turner EH, Matthews AM, Linardatos E, Tell RA, and Rosenthal R. (2008), "Selective publication of antidepressant trials and its influence on apparent efficacy", *New England Journal of Medicine* 358, pp. 252-260.

See also Doornbos B, de Jonge P, Bockting CLH. (2008), "Selectieve publicatie van onderzoek met antidepressiva: gevolgen voor de richtlijn 'Depressie'", *Ned Tijdschr Geneesk.*, 2008, 21 June, 152(25), pp. 1406-1408.

14 McGauran N, Wieseler B, Kreis J, Schüler Y-B, Kölsch H, Kaiser T. (2010), "Reporting bias in medical research – a narrative review", *Trials*, 2010, 11:37, 15 p.

See web page: [www.trialsjournal.com/content/11/1/37](http://www.trialsjournal.com/content/11/1/37)

This article includes a list of over 250 reference articles, some of which restate the references given in the NIHR report 2010.

were underreported, positive secondary outcomes were highlighted rather than negative primary outcomes<sup>15</sup>.

Numerous studies have been conducted comparing publication bias. The NIHR report 2010 contains a list of 537 reference articles. One of the objectives of the *health technology assessment* was in fact to identify and assess empirical studies on publication bias and related bias published as of 1998.

It is also important that the outcome variables or the assessment criteria in the context of a clinical study are chosen carefully and that the limitations on variables or criteria are explained. Hochman et McCormick<sup>16</sup> thus stress that without any explanation of their limitations, the use of substitution criteria<sup>17</sup> or combined assessment criteria rather than clinical criteria, or of mortality due to illness rather than total mortality or the reporting of relative risks rather than absolute risks can lead to biased findings, which complicates the way they are interpreted by the doctors, the patients and the political decision-makers.

An article by Lexchin et al.<sup>18</sup> states that studies of medicinal products sponsored by pharmaceutical companies generate more positive research findings than the same studies on medicinal products conducted by researchers who are not working on behalf of the pharmaceutical industry.

In his article, Steen<sup>19</sup> indicates that 85 % of clinical trials sponsored by the industry result in positive findings, as against 50 % for studies financed by public funds. It is also possible that this is linked to the fact that the industry examines more advanced study phases when a positive outcome is more probable than in the initial phase of a research project.

#### *Need for adequate reporting*

It is important to report clinical trials adequately for both scientific and ethical reasons.<sup>20</sup> Failing to publicly disclose findings that are 'unfavourable', 'of no interest', or not presenting sufficiently detailed findings (underreporting/selective reporting) can mean that patients are given treatment that is ineffective, or even harmful, for longer than is necessary or that they are refused a more effective treatment for longer than is necessary.<sup>21</sup>

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15 First of all, the primary and secondary outcome variables defined in advance – that is prior to the execution of the research – must be distinguished from outcome variables determined by 'post hoc analysis'. The definition given below concerns the outcome variables cited first: see [www.consort-statement.org/resources/glossary/m---p/outcome-primary-and-secondary/](http://www.consort-statement.org/resources/glossary/m---p/outcome-primary-and-secondary/):

"outcome, end point: An outcome variable of interest in the trial (also called an end point). Differences between groups in the outcome variable(s) are believed to be the result of the differing interventions. The primary outcome is the outcome of greatest importance. Data on secondary outcomes are used to evaluate additional effects of the intervention."

16 Hochman M, McCormick D. (2011), "End point selection and relative (versus absolute) risk reporting in published medication trials", *Gen Intern Med*, 6(11):1246-52, DOI: 10.1007/s11606-011-1813-7.

17 Arterial tension figures with, as clinical criterion, morbidity/mortality – are an example of a substitution criterion.

18 Lexchin J, Bero LA, Djulbegovic B, Clark O. (2003) "Pharmaceutical industry sponsorship and research outcome and quality: systematic review, *BMJ*, 31 May 2003, vol. 329, pp. 1167-1170.

19 Steen GR. (2011), "Misinformation in the medical literature: what role do error and fraud play?" *JMedEthics*, 2011, vol. 37, pp. 498-503, see p. 502.

20 See Chalmers, I., "Underreporting research is scientific misconduct", abridged version in *Ethical and regulatory aspects of clinical research: readings and commentary*, Ezekiel, J.E. et al., Johns Hopkins University Press, 2003, pp. 411-414, see p. 411-412. [The article was initially published in *JAMA* 263 (1990), pp.1405-1408]

See also NIHR report 2010, p. X.

See also Rennie D. (2008), "The obligation to publish and disseminate results", in *The Oxford textbook of clinical research ethics*, Ezekiel JE et al., Oxford University Press, pp. 795-807, see p. 795.

See also Strech D. (2012), "Normative arguments and new solutions for the unbiased registration and publication of clinical trials", *Journal of Clinical Epidemiology* (Elsevier), 65 (2012) pp. 279-281 [Epub 2011 Oct 18/19] – web page: [www.open-project.eu/publications](http://www.open-project.eu/publications).

21 See also NIHR report 2010, pp. 39-40.



Patients and healthy volunteers who take part in clinical trials make an important contribution to progress in scientific knowledge. Inadequate reporting and the non-publication of all the findings do not do justice to those who take part in trials voluntarily in a spirit of altruism.

Another consequence of this may be that limited resources and funds are not used to best effect and are therefore wasted.

Moreover, this jeopardises the integrity of scientific research. When striking research findings are more widely disseminated than inconclusive findings, this represents a threat to the validity of a research synopsis.<sup>22</sup>

#### *Which players are involved?*

The NIHR 2010 report stipulated that underreporting of research findings or a publication bias may result from a convergence of the interests of the researchers, peer reviewers, editors and sponsors, while at the same time pointing out that they may be responsible to differing degrees. Despite the fact that various complex factors play a role in the phenomenon of publication bias, the NIHR report states that it is possible to prevent publication bias to a certain extent and reduce its impact. The report puts forward measures to this end, including an adaptation of the policy on the publication of research findings, the possibility of electronic publication, an open access policy, the prospective registration of studies and the setting up of large-scale studies to confirm small-scale research findings.<sup>23</sup>

The World Medical Association also sets out in Article 30 of the sixth version of the Declaration of Helsinki (Seoul, October 2008) a series of ethical obligations for the players concerned:

"Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."<sup>24</sup>

Iain Chalmers<sup>25</sup> also stresses the responsibility of research ethics committees. These committees do but half their job when they approve a clinical trial, but do not then check whether the study is undertaken in line with the dossier submitted and whether the research findings have been adequately reported.

On the basis of the NIHR report 2010, it may be concluded that the underreporting of research findings is a complex problem, which is important given the impact it exerts on the integrity of scientific research. Many articles as well as the NIHR report single out the need to

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See also Sandercock P. (2011 copyright) "Negative results: why do they need to be published?", *International Journal of Stroke*, Vol 7, January 2012, pp. 32-33, see p. 32.

See web page: [onlinelibrary.wiley.com/doi/10.1111/j.1747-4949.2011.00723.x/full](http://onlinelibrary.wiley.com/doi/10.1111/j.1747-4949.2011.00723.x/full).

22 NIHR report 2010, p. X.

23 NIHR report 2010, p. 50-51.

24 Original version: "Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."

25 Chalmers I. "Underreporting research is scientific misconduct", abridged version in *Ethical and regulatory aspects of clinical research: readings and commentary*, Ezekiel JE et al., Johns Hopkins University Press, 2003, pp. 411-414, see pp. 413-414.

(1) register the protocol data in public registers (including the definition of primary outcomes) in advance and (2) make all research findings accessible.

## 1.2. Prospective registration in a public register

The registration of clinical trials in a public register before they begin is a first step that make it possible to detect underreporting or a publication bias and check whether there is risk of the biased presentation of scientific discoveries. Once this registration has been done, it is in fact possible to check later on whether the findings of a clinical trial have been published or publicly disclosed. It is also possible to detect whether the trial is still ongoing or has been prematurely interrupted and why. The reported research findings can also be compared with the research assumption or assumptions initially registered.<sup>26</sup>

It should be noted that in the sixth version of the Declaration of Helsinki (Seoul, October 2008), a new Article 19 was inserted which expressly mentions the need for the prospective registration of clinical trials: (free translation)

"Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."<sup>27</sup>

In a working document<sup>28</sup> from the World Health Organisation (WHO), the following advantages are associated with the prospective registration of clinical trials in public registers:

- this registration is likely to be facilitate the recruitment of participants in clinical trials as it is also a means of informing potential participants and care providers of the existence of studies;<sup>29</sup>
- the pointless duplication of a study already underway elsewhere can be avoided.

The 2010 annual report from the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek*, CCMO) also stresses that patients are increasingly showing an interest in research relating to 'their' illness and sometimes seek specifically to take part in clinical trials through which they can access innovative treatments.<sup>30</sup>

This transparency also enables promoters to deploy their resources in areas of study where there is still little evidence-based knowledge. Those who produce summaries of research findings, including the authors of systematic reviews, meta-analyses and practice guidelines, can thus efficiently and univocally identify all the trials that have been conducted or are still ongoing in their field of interest.<sup>31</sup>

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26 Idem, see p. 414.

See also NIHR report 2010, p. 53.

See also Askie L, Gherzi D, Simes J. (2006), "Prospective registration of clinical trials", *Australian Journal of Physiotherapy*, vol. 52, pp. 237-239, see p 237.

27 Original version: "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."

28 Gherzi D, Clarke M, Berlin J, Gülmezoglu AM, Kush R, Lumbiganon P, Moher D, Rockhold F, Sim I, Wager E. (2008), "Reporting the findings of clinical trials: a discussion paper", *Bulletin of the World Health Organization*, 86(6), pp. 492-493, see p. 492.

See also Chalmers I, Altman DG. (1999), "How can medical journals help prevent poor medical research? Some opportunities presented by electronic publishing", *Lancet*, vol. 353, pp. 490-493, see p. 491.

29 See also "WHO clinical trials initiative to protect the public", *Bulletin of the World Health Organization*, January 2006, 84(1), pp. 10-11, see p. 11.

See also Askie L, Gherzi D, Simes J. (2006), "Prospective registration of clinical trials", *Australian Journal of Physiotherapy*, vol. 52, pp. 237-239, see p. 237.

30 CCMO Annual report 2010, p. 32.

31 See also Askie L, Gherzi D, Simes J. (2006), "Prospective registration of clinical trials", *Australian Journal of Physiotherapy*, vol. 52, pp. 237-239, see p 237.

As explained in the following point, the interest of the prior or prospective registration of clinical trials (phase II, III and IV trials<sup>32</sup>) is acknowledged on various sides. As regards the disclosure of information on phase I trials or *first-into-man studies*, however, there is more discussion.<sup>33</sup>

#### *Existing initiatives, points of view and guidelines*

There follows a non-exhaustive survey of a number of initiatives and points of view/guidelines concerning the prospective registration of research protocols. Some of these are covered in more detail in Annex 1.

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32 The four successive phases of clinical trials are described in the introductory report to Opinion No 13 of 9 July 2001 on human experimentation, issued by the Committee, as follows (see point B. Definitions):

“Phase I involves administering the product for the first time, in principle to a small number of volunteers in good health [editor’s note: often healthy volunteers, but not always, for example in the case of anti-cancer products], to assess their tolerance to the product, determine the maximum tolerated by humans and the minimum active dose of the product, and study its pharmacokinetic and pharmacodynamic properties.

Phase II concerns trials on a limited group of patients suffering from the pathology for which the product is intended, in order to confirm its efficacy, assess its therapeutic interest, assess the relationship between the risks and the advantages linked to its administration and seek the best dose and the best means of administration depending on the effect sought.

During phase III, studies are conducted on a large number of patients, usually divided into comparable groups, according to a strict methodology (randomisation). These studies aim to examine tolerance in the medium term and efficacy, so as to be able to estimate the relationship between the benefits and the disadvantages (unwanted effects and cost). This phase is also used to gather information which will be useful for prescribers. If it proves conclusive, the next step is to think about marketing the product and fulfilling the procedures to issue the authorisation to place it on the market.

Phase IV comprises the studies conducted once the product has been put on the market. These studies are used to gain better knowledge of the product: the possible association with other therapeutics, the discovery of new actions, the rare or related side effects, etc.”

33 NIHR report 2010, p. 83.

See also Annex 3, point 3. Scope of application: “The information to be included in the EudraPharm database further to section 4 covers clinical trials, phases II, III et IV, (...).”

### The European Union (EMA)

Protocols on interventional clinical trials with medicinal products that fall under the scope of application of European Directive 2001/20/EC, must be registered prospectively in the EudraCT database. In early 2011, the Clinical Trials Register<sup>34</sup> was launched in which the European Medicines Agency (EMA) makes public several field of information in the EudraCT database. The European Commission describes the interest of this procedure as follows:

“This information is potentially useful for patients, care staff and the health professionals, who may be interested in the trials that are underway and trials that have already been carried out. Moreover, more transparent information can contribute towards the development of research and thus guarantee the devising of better quality trials, requiring the participation of a smaller number of patients and avoiding all needless duplication. The pharmaceutical industry, university and scientific circles as well as the regulatory bodies are other potential users of this type of information.”<sup>35</sup>

### The United States (FDA)

In the United States, since February 2000 there has been a similar public register at the *Food and Drug Administration* (FDA) where clinical trials are recorded before they begin, see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### The World Health Organisation (WHO)

The World Health Organisation is also endeavouring, with its International Clinical Trials Registry Platform (ICTRP) to produce a comprehensive list of clinical trials with a view to guaranteeing greater transparency and validity of evidence-based scientific knowledge.<sup>36</sup>

The WHO also defines a clinical trial more broadly than European Directive 2001/20/EC (see also Annex 1, B.2.).

### The Netherlands (CCMO)

Like Belgium, the Netherlands has national legislation with a wider scope of application than that of European Directive 2001/20/EC.

In the Netherlands, the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek*, CCMO) collects, data from research protocols assessed by recognised medical-ethical assessment committees (*Medisch-ethische toetsingscommissies*, METC), as well as their decisions via the portal <https://ToetsingOnline.ccmo.nl>. For new studies which, as of 1 November 2009, are submitted for assessment to the METC, the basic data from the *Algemeen Beoordeling- en Registratieformulier* (ABR-formulier, General assessment and registration form) are automatically made public as soon as they are entered into *ToetsingOnline* by the METC which assessed the study. As of 2010, an exception is made for phase-1 studies: the basic data from the ‘ABR’ form are not automatically made public when entered *ToetsingOnline* by the METC concerned, but six months later<sup>37</sup>. (See Annex 1, C.).

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34 <https://www.clinicaltrialsregister.eu>

35 See annex 3, point 1. Introduction; end of second paragraph.

36 See [www.who.int/ictrp/en](http://www.who.int/ictrp/en): “The mission of the WHO International Clinical Trials Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.”

37 CCMO annual report 2010, p. 32 –web page: [www.ccmo-online.nl/hipe/uploads/downloads\\_catc/CCMO%20jaarverslag%202010.PDF](http://www.ccmo-online.nl/hipe/uploads/downloads_catc/CCMO%20jaarverslag%202010.PDF)

## Belgium (the Advisory Committee on Bioethics and the FAMHP)

In Belgium, there are currently two websites on which information relating to clinical trials (experiments) are registered, but these are not accessible to the public.

The Advisory Committee on Bioethics manages a website on which medical ethics committees (MEC) report annually on their activities a posteriori. The title and characteristics of experiments submitted to MECs for an opinion are thus reported. This includes both experiments that fall under the Belgian act of 7 May 2004 on human experimentation and those that are not covered by its scope of application. The MECs also report on the ethical topics they have covered. On the basis of these data, the Advisory Committee on Bioethics draws up an annual report on the activities of the MECs. This a posteriori report only includes approved data.

As regards experiments that fall under the Belgian act but are not interventional clinical studies with medicinal products as referred to in European Directive 2001/20/EC<sup>38</sup>, a unique Belgian number has to be requested in advance on a website run by the Federal Agency for Medicines and Health Products (FAMHP).

Interventional clinical studies on medicinal products referred to by the European directive<sup>39</sup> must be prospectively recorded in the EudraCT database, in which a number of information fields are open for public consultation via the Clinical Trials Register.

It should be stressed that a project is underway within the FAMHP with a view to developing an interactive website<sup>40</sup> for the registration and follow-up of clinical trials.

### The editors (ICMJE)

A major initiative has also been taken in the world of publishing. Further to the decision of the International Committee of Medical Journal Editors (ICMJE), in 2004, to henceforth accept for publication only clinical trials that have undergone prospective registration<sup>41</sup> in a recognised public register, an increase of over 70 % in the number of clinical trials registered was observed in 2005.<sup>42</sup> (See also Annex 1, B.4.).

### The pharmaceutical industry (IFPMA)

The pharmaceutical industry acknowledges the interest of granting health-care providers, patients and others access to information on clinical trials while stressing the need to take account, when disclosing such information, of privacy, intellectual property rights and contract law. (See also Annex 1, B.7.).

### *Some observations*

Prospective registration can only contribute toward greater transparency in scientific research when the data are registered in full and are, moreover, significant. A study conducted on 5 % of the clinical trials registered prospectively between, June 2008 and June 2009 in a register that is part of the WHO *International Clinical Trials Registry Platform*

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<sup>38</sup> In other words, all experimentation falling under the application of the Belgian act of 7 May 2004 on human experimentations, to the exclusion of clinical trials.

<sup>39</sup> In other words, clinical trials as defined in the Belgian act of 7 May 2004 on human experimentation.

<sup>40</sup> See also Circular No 512 from the FAMHP (2008), point 3: "The interactive website is intended to improve communication between the various parties involved for the approval of an experiment (promoter – lead ethics committee – local ethics committee – FAMPH)." – see website: [www.fagg-afmps.be/fr/items/circulaires/2002-2008/](http://www.fagg-afmps.be/fr/items/circulaires/2002-2008/)

<sup>41</sup> Both the ICMJE and the WHO define prospective registration as the recording of the clinical trial in a register before the recruitment of the first person involved in the research.

<sup>42</sup> NIH report 2010, p. 54 [with reference to Zarin DA, Tse T, Ide NC. (2005), "Trial registration at ClinicalTrials.gov between May and October 2005", *N Engl J Med* 2005; 353:2779987].

(ICTRP), showed that important data are often lacking or are incomplete or devoid of meaning<sup>43</sup>. (See also Annex 1, point B.2.).

According to the NIHR report 2010, such registers only become useful when the data are used by the authors of systematic reviews and meta-analyses in their research and can be compared with their findings<sup>44</sup>. It is then possible to effectively detect the clinical trials for which no research results are known and the reason for this can be determined (still ongoing, premature close, etc.)<sup>45</sup> or the findings published can be checked on the basis of the preliminary research assumption and the primary/secondary outcomes described in the protocol, or with full study data.

### *Some conclusions*

An initial, essential stage to prevent underreporting or a publication bias as regards research findings consists of moving towards worldwide prospective registration of clinical trials – in their broadest definition and including basic research. This registration will only really be able to contribute towards greater transparency if the data registered are complete and significant, and they are also kept up to date. It further emerges from the ICMJE initiative that prospective registration is only effective if it is binding.

## 1.3. Publication of all research findings

Meticulous prospective registration of clinical trials alone is not enough to guarantee the transparency of scientific research. Research findings must be and remain permanently accessible and should ideally be kept by an independent body.

Ideally, all clinical trials should be recorded in public registers as soon as they start. All the research findings should then also be kept there. In fact, all new studies follow on from research carried out previously.

The pharmaceutical industry acknowledges the interest of prior or prospective registration of clinical trials, but expresses reservations as to information that is sensitive in terms of competition<sup>46</sup>. As regards the publication of research findings, the pharmaceutical industry is more cautious, for the time being standing by the publication of findings from phase IV trials and, by extension, phase III trials. (See Annex 1, B.7.). The industry also stresses, rightly, the importance of protecting intellectual property rights and contract law. Premature communication of research findings, for example before a patent procedure has been settled, risks causing a company to lose a major competitive advantage.

To achieve greater transparency in scientific research, Spielmans and Parry<sup>47</sup> suggest in their article that better access to all raw research data should be promoted. The clinical trials registers in which protocols are registered in advance have not resolved the problem of underreporting or selective reporting. Publishers, peer reviewers, etc. should ideally check that the data published correspond to the 'raw' research findings and the protocol registered beforehand. The reports which are forwarded to regulatory bodies such as the FDA should

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43 Viergever RF, Ghersi D. (2011), "The quality of registration of clinical trials", PLoS ONE, February 2011 6(2), e14701, pp. 1-8 – web page:

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014701>

44 NIHR report 2010, p. 83.

45 NIHR report 2010, p. 56.

46 See annexe 1, B.2.: The pharmaceutical industry puts forward objections to the prospective publication of information in information fields 10, 13, 17, 19 and 20, but the WHO stands by to the prospective registration and publication of all these points. The fields of information in question are: 10. Scientific Title - 13. Intervention(s) - 17. Target Sample Size - 19. Primary Outcome(s) - 20. Key Secondary Outcomes.

47 Spielmans GI, Parry PI. (2010), "From evidence-based medicine to marketing-based medicine: evidence from internal industry documents". *Journal of Bioethical Inquiry*, Springer, 2010( 7), pp. 13-29 – see web page: [i.bnet.com/blogs/spielmans-parry-ebm-to-mbm-jbioethicinqu-2010.pdf](http://i.bnet.com/blogs/spielmans-parry-ebm-to-mbm-jbioethicinqu-2010.pdf)

also be made public as discrepancies are often observed between the data reported there et those published in medical-scientific reviews.<sup>48</sup>

Not only pharmaceutical companies, but also editors have commercial interests that need to be balanced against the advantages of broad access to precise data for science. Thus editors, too, wish to be able to control the dissemination of research findings (see Annex 1, B.4., not. Ingelfinger rule) and they point to the need for peer reviews<sup>49</sup> to guarantee quality. Moreover, they also favour the publication of clinical trials accompanied by 'positive' findings<sup>50</sup>.

Spielmanns and Parry refer in their article to a possible solution devised by Richard Smith, a former editor of the *British Medical Journal*. His proposal consists of publishing the protocols of studies and their findings in an online register only, and publishing solely articles that discuss the validity of these studies in scientific periodicals. This may seem to be a curious solution, but according to the two authors, it has not really been proved that peer review results in clearly better reporting of research findings.<sup>51</sup>

In this context, the NIHR report 2010 points out that electronic publication offers the possibility of unlimited publication space so that more information and data could be made accessible. Studies could thus be judged on their design and methodology, as well as the immediate relevance of findings in practice. The editors of electronic reviews could also encourage the publication of studies with negative or inconclusive findings.<sup>52</sup>

Finally, it may be asserted that transparency is also essential to detect scientific fraud, such as deliberately holding back negative findings or the distortion of research data.

#### *Existing initiatives, points of view and existing guidelines*

There also follows a non-exhaustive survey of a certain number of initiatives and existing points of view/guidelines at international and European level to promote the publication of research findings. Some of these are covered exhaustively in Annex 1.

#### The United States (FDA)

As indicated above, since February 2000 there has been a public register in the United States in which clinical trials are registered before they start. In 2007, the *Food and Drug Administration Amendments Act* (27 September 2007) expanded this register to include the findings of these clinical trials. (See also Annex 1, B.1.).

In addition, in 2011, a sub-committee of the *US Presidential Commission for the Study of Bioethical Issues*, that is the '*International Research Panel*' recommended in particular<sup>53</sup>

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48 Idem, see pp. 25-26.

49 NIHR report 2010, pp. 51-52.

50 Spielmanns GI, Parry PI. (2010), "From evidence-based medicine to marketing-based medicine: evidence from internal industry documents". *Journal of Bioethical Inquiry*, Springer, 2010(7), pp. 13-29, see p. 26.

51 Idem, see p. 26 [with reference to Jefferson T, Rudin M, Brodney Folse S, Davidoff F. (2007) "Editorial peer review for improving the quality of reports of biomedical studies", *Cochrane Database of Systematic Reviews* 2].

52 NIHR report 2010, pp. 52-53.

See also Chalmers I. "Underreporting research is scientific misconduct, abridged version in *Ethical and regulatory aspects of clinical research: readings and commentary*, Ezekiel JE et al., Johns Hopkins University Press 2003, pp. 411-414, see pp. 413-414.

See also Sandercock P. (2011 copyright) "Negative results: why do they need to be published?", *International Journal of Stroke*, Vol. 7, January 2012, pp. 32-33, see p. 33.

Web page: [onlinelibrary.wiley.com/doi/10.1111/j.1747-4949.2011.00723.x/full](http://onlinelibrary.wiley.com/doi/10.1111/j.1747-4949.2011.00723.x/full).

53 "US commission recommends increased protection for people in research after reviewing 1940s syphilis study", *BMJ* 2011; 343.d5577 (published 2 September 2011) – original version: "Greater transparency and monitoring of research are needed to hold investigator and institutions responsible and accountable for violations of rules, standards and practices."

that the states should think about making the registration of all research studies comprising a more than minimal risk and the publication of their findings mandatory. Similarly, greater transparency and closer control of research are needed to be able to make researchers and research institutions responsible for the infringement of rules, standards, etc.

#### The European Union (EMA)

As also mentioned above, on 22 March 2011, the European Medicines Agency (EMA) launched the Clinical Trials Register (<https://www.clinicaltrialsregister.eu>) in which information fields from protocols that have been prospectively registered in the EudraCT database are published. Public consultation of the findings of all clinical trials registered is not yet possible at the moment, but according to a draft text from the European Commission dated 1 June 2010<sup>54</sup> which has been submitted for public consultation, this is the aim<sup>55</sup>. For clinical trials, the proposal is for the findings to be sent to the EMA at the latest twelve months after the end of the trial – whether this ended as planned or was interrupted prematurely – so that the EMA can include the findings in the EudraCT database. For paediatric trials, this period is reduced to six months. The findings should also be accessible to the public via the Clinical Trials Register within five working days after a validated data set has been sent to the EMA (see below, Annex 1, A.2.).

The OPEN project jointly funded by the European Commission (7th framework programme) was started up at the end of 2011. This two-year project ran from 1 November 2011 to 31 October 2013. Its main aim was to examine the possibilities of overcoming the underreporting of negative findings (to Overcome the failure to Publish nEgative fiNDings”). The partners, objectives and findings referred to and the various work packages are described on the website [www.open-project.eu](http://www.open-project.eu). The fourth work package will comprise an assessment of the policy and procedures of medical ethics committees as regards the prevention of publication bias.<sup>56</sup>

#### The Council of Europe (European Convention on Human Rights and Biomedicine)

In the additional protocol to the Oviedo Convention on Human Rights and Biomedicine, relating to biomedical research, the Council of Europe also devoted an article to the availability of research findings. The principles of this were developed further in the guide published recently and intended for the members of ethics committees who assess protocols. In this guide, the Council of Europe also covers the role of these committees, in that they have to ensure that research findings are made public. We will return to this in more detail in point 2 concerning the ‘Role of medical ethics committees’.

#### The World Health Organisation (WHO)

Within the World Health Organisation, a working group has reached the following conclusion (see below, Annex 1, B.2.):

"The findings of all clinical trials must be made publicly available".<sup>57</sup>

#### The World Medical Association (WMA) Declaration of Helsinki

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*Governments should consider requiring all research involving more than minimal risk to be registered and results reported”.*

54 Document of 1 June 2010 bearing reference SANCO/C/8/SF D(2010) 326416: Implementing technical guidance – List of fields for result-related information to be submitted to the 'EudraCT' clinical trials database, and to be made public, in accordance with Article 57 (2) of Regulation (EC) No 726/2004 and Article 41 of Regulation (EC) No 1901/2006 and their implementing guidelines 2008/C168/02 and 2009/C28/01, Draft – submitted for public consultation. See page web: [http://ec.europa.eu/health/files/clinicaltrials/technical\\_guidance\\_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/technical_guidance_en.pdf)

55 This register will be developed gradually.

56 “Work Package 4: Evaluation of policies and procedures of research ethics committees to prevent and monitor publication bias.”

57 Original version: “The findings of all clinical trials must be made publicly available”.



As already mentioned, in the sixth version of the Declaration of Helsinki (Seoul, October 2008), Article 30 stresses the interest of complete transparency in the publication of the findings of clinical research and states that the authors, editors and publishers all have ethical obligations as regards the publication of research findings.<sup>58</sup>

### Scientific organisations

The 'Code of ethics of scientific research in Belgium'<sup>59</sup> is a joint initiative of the *Academie Royale des Sciences, des Lettres et des Beaux Arts de Belgique*, the *Academie Royale de Médecine de Belgique*, the *Koninklijke Vlaamse Academie van België voor Wetenschappen en Kunsten* and the *Koninklijke Academie voor Geneeskunde van België*, supported by the *SPP Politique scientifique*. This code sets out the main principles of ethically justified scientific practice.

European scientific organisations also stress the need to make publicly available all the findings of clinical trials and to this end, to develop integrated databases for clinical research. (See Annex 1, B.5 et B.6).

The CONSORT group is an international network which includes researchers (trialists), methodologists and editors of specialised medical reviews. This group has drawn up a declaration – the most recent *CONSORT statement* dated from 2010 – setting out a minimum set of evidence-based recommendations for the reporting of randomised clinical trials (RCTs) ([www.consort-statement.org](http://www.consort-statement.org)).

The EQUATOR project also grew out of this group in 2006. It aims to improve the reliability and value of medical research literature by promoting the transparent and precise reporting of studies. The EQUATOR network was officially inaugurated in London in 2008 ([www.equator-network.org](http://www.equator-network.org)). This umbrella organisation includes researchers, editors of specialised medical reviews, peer reviewers, developers of reporting guidelines, research funding bodies, in short everyone who has an interest in improving the quality of research **and** research publications.

It is also worth noting that in 2002, the open access peer-reviewed online *Journal of Negative Findings in Biomedicine*, was introduced.<sup>60</sup>

### Some conclusions

Many bodies see the interest of making all research findings accessible: not only generally 'positive' findings which are published in scientific reviews, but also inconclusive or negative findings, or all 'raw' research findings (raw data). Complete transparency of scientific discoveries also proves necessary to promote medicine that is truly evidence based. Given this interest, however, it is also necessary to take account of the real commercial and economic interests of the pharmaceutical industry, in particular. Nevertheless, more and more initiatives are being taken that aim to achieve complete transparency in research findings.

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58 For more details, see point 1.1. Underreporting of research results – Who is involved?

59 See [www.belspo.be/belspo/organisation/publ/Eth\\_code\\_fr.stm](http://www.belspo.be/belspo/organisation/publ/Eth_code_fr.stm)

60 NIHR report 2010, p. 53.

See also web page: [www.jnrnm.com](http://www.jnrnm.com): "Journal of Negative Results in BioMedicine is an open access, peer-reviewed, online journal that promotes a discussion of unexpected, controversial, provocative and/or negative results in the context of current tenets."

## 2. ROLE OF MEDICAL ETHICS COMMITTEES

In the context of the ethical examination of a protocol on human experimentation, can/must a medical ethics committee check in what way the research findings – whether positive, negative or inconclusive – will be published or made publicly available? This is the request for an opinion as reformulated by the Committee.

The Council of Europe and the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek*, CCMO) have recently considered this question.

### 2.1. Guide from the Council of Europe intended for Research Ethics Committees (REC) <sup>61</sup>

On 7 February 2011, the Council of Europe published a guide intended for the members of research ethics committees (REC). Article 28 of the additional protocol to the Oviedo Convention on Human Rights and Biomedicine relating to biomedical research already states that when a research project is over, a report or a summary should be drawn up to be forwarded to the medical ethics committee or the competent authorities.

The guide refers above all to interventional studies carried out on human subjects. However, it may be supposed that some points, such as access to research findings, are relevant for all biomedical and scientific research projects in which human subjects are involved.<sup>62</sup>

The guide distinguishes three research stages<sup>63</sup>. Below, some of the recommendations in the guide are briefly compared with the provisions in European Directive 2001/20/EC on interventional studies involving medicinal products and the Belgian act of 7 May 2004 on human experimentation<sup>64</sup>.

#### **a. Before the research starts**

The guide states that the RECs should assess the ethical acceptability of biomedical research projects ('their main objective').

#### **b. During the research**

According to the guide, the RECs should follow up the research projects they have approved and may need to re-examine them owing to new and relevant knowledge acquired during the research.

#### **c. After the research**

The guide states that the role of the REC in this stage is still fairly limited:

"The role of the REC, once the research is over, is currently limited [...]. It is generally considered that this is not the period when recourse to the expertise of the REC is the most important. Moreover, the RECs rarely have the legal competence, the time and other resources to work effectively to this end."

However, the guide states that the RECs should also check whether a transparent report has been drawn up on the results of the research projects they have examined:

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61 See also annexe 1, B.3. and web page:

[www.coe.int/t/dg3/healthbioethic/source/INF\(2011\)\\_fr.pdf](http://www.coe.int/t/dg3/healthbioethic/source/INF(2011)_fr.pdf)

62 Guide for the members of research ethics committees, 1. The guide: a tool for the members of research ethics committees (REC), paragraph 2.

63 Guide for members of research ethics committees, 5.A.1. Roles and activities of RECs in the research process.

64 This act transposes the provision of European directive 2001/20/EC.

“Another ethical obligation of researchers or the promoters of research is to make the conclusions of the research accessible to the public by publishing them in full using a suitable means. Sometimes, research findings, in particular ‘negative’ research findings are suppressed; such biased publication is not only contrary to the scientific and ethical requirements but also harms patients, for example when unwanted side effects are concealed. Even though several mechanisms have been put in place to improve the transparency of the information reports on research, for example, the obligation to register all clinical trials on medicinal products in a public database before the trials begin (see Chapter 6 – Independent examination of a research project by an REC), the RECs can still help focus on this important issue when research projects that they have examined have finished.”

Belgian law stipulates that the medical ethics committee that had issued a opinion positive about an experiment must be informed when it is over. In the case of an interventional study with medicinal products, the competent national body (the Federal Agency for Medicine and Health Products) must also be informed when a project has finished. In this case, the end of the study is also included in the EudraCT database. The Clinical Trials Register also indicates, per protocol, whether the study is ongoing or finished. Neither the Belgian act nor the European directive provides for mandatory publication of the research findings. As has already been mentioned in point 1.3., the ultimate intention is, however, to include the research findings of clinical trials registered prospectively in this database in the EudraCT database as well, and make them partially public via the Clinical Trials Register.

Chapter 6 of the guide focuses on the content of an **independent examination of a research project by an REC**. Point 6.C concerns the information to be provided to the REC, which this body has to examine. This information includes the research findings (6.C.20) for which the following recommendations are made:

- **making research findings available to the REC and participants:**  
“[...] when the research is over, the researchers must send the REC a report or a synopsis of the findings obtained. It is also at this stage that the researchers should confirm their initial proposals concerning the publication of the findings in scientific journals or making them publicly available by other means.  
The general research conclusions should be made accessible to all participants who so wish, in an understandable form. If the communication of this information also has to respect the interests of third parties, such as the promoter of the research or the researchers themselves, this should not constitute an argument to deprive participants of their legitimate right to know the result of the research in which they took part. However, a reasonable period of time may be acceptable.”

Neither the European directive nor the Belgian act expressly mention that at the end of the experiment (which must be reported), the findings also have to be made available to the medical ethics committee that issued a favourable opinion for the research project or the competent authority in the case of an interventional study with medicinal products (FAMHP) or the participants in the trial.

As we have already mentioned, a draft text from the European Commission proposes that in future, the findings of clinical trials should be made publicly available via the Clinical Trials Register at the latest twelve months after the end of the trial – whether it was completed or interrupted prematurely. For paediatric trials, this, this period of time is reduced to six months. (See Annex 1, A.2.).

- **publication of research findings for scientific and health-care purposes:** (extract from the Council of Europe guide)

“It is important to make research findings publicly available, irrespective of whether the research assumption has been confirmed (positive result) or invalidated (negative result) or these findings do not lead to a conclusion.” [...]

The additional protocol to the Oviedo Convention on biomedical research makes it mandatory for researchers to submit a report or a summary to the REC at the end of the study. Should study end prematurely, a report including the reasons for this should also be submitted to the REC. Moreover, the protocol requires the publication of findings within a reasonable period of time, as well as the communication of the conclusions of the research to participants who so request. The REC must therefore have access to elements enabling it to ensure that the researchers have defined a publication policy, that they have discussed the matter with all external promoters so that they are not prevented from publishing the findings owing to contractual obligations. A reasonable period of time for publication is acceptable, in not order to adversely affect a patent application. However, this argument should not constitute a pretext for the unlimited retention of the findings.

Particular concerns have been expressed regarding the publication of research findings on potential new treatments, biased notably owing to the concealment of ‘unfavourable’ findings. To overcome this practice and ensure that the findings are published, researchers should register all research projects before they begin in a register that is accessible to the public. The members of the REC can encourage this effort at transparency by making this registration a condition for their positive opinion regarding the ethical acceptability of the research project. Although national legislation does not allow the opinion to be conditioned by a request like this, the REC should at least use its position to request that all the findings be made publicly available.”

Neither European Directive 2001/20/EC nor the Belgian law of 7 May 2004 expressly mentions that a medical ethics committee is competent to monitor the publication policy adopted for a research project. In the Netherlands, this provision is, however, made.

## 2.2. Directive from the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek, CCMO*)

On 13 November 2008, the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek, CCMO*) published the ‘Research contract assessment’ directive (*Richtlijn ‘Beoordeling onderzoekscontract’*) intended for medical-ethical assessment committees (*Medisch-ethische toetsingscommissies, METC*), which entered into force in 2009. In 2010, this directive was assessed, resulting on 30 August 2011 in the revised ‘Research contract assessment’ directive<sup>65</sup>. Article 3 became Article 4, in which point c) was reworded and point d) added.

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65 Revised CCMO ‘Research contract assessment’ directive of 30 August 2011: [www.ccmo-online.nl/hipe/uploads/downloads\\_catc/CCMO%20jaarverslag%202010.PDF](http://www.ccmo-online.nl/hipe/uploads/downloads_catc/CCMO%20jaarverslag%202010.PDF)

(initial CCMO ‘Research contract assessment’ directive of 13 November 2008: [www.ccmo-online.nl/hipe/uploads/downloads\\_catp/Staatscourant%20CCMO-richtlijn%20onderzoekscontracten.pdf](http://www.ccmo-online.nl/hipe/uploads/downloads_catp/Staatscourant%20CCMO-richtlijn%20onderzoekscontracten.pdf))

(free translation<sup>66</sup>)

**“Article 4**

The contract may not include unreasonable limitations regarding the publication of research findings. Unreasonable limitations are deemed to mean in any case:

- a. the condition that publication is authorised only after the approval of the promoter or the investigator;
- b. the right of the promoter or the investigator to ban publication by another party without giving a reason for this or giving a reason that does not offset the importance of data publication;
- c. a ban on the publication of data or some data on condition that the planned publication is submitted to the other party when the period of application of this ban exceeds ninety days, subject to special conditions which may justify a longer period;
- d. a ban or limitations on the publication of data or some data which is extended beyond twelve months after the end of the research in the absence of publication of the findings;
- e. an exclusive right of publication for the promoter or the investigator unless this is not considered unreasonable in a given situation.”

This article is accompanied by the following comment: (free translation)

“The directive notes [...] that unreasonable limitations on publication are unacceptable [...]. The contracting parties are of course free to agree terms of publication provided that the starting point is that the data will be made publicly available and that one of the parties does not have its possibilities of publishing the findings itself unreasonably limited. The limitation that, in the event of multi-centre research, individual researchers will not publish their findings until after the central publication of all the data may be considered reasonable, provided that this central publication takes place within a reasonable period of time. A period of longer than 12 months will be considered unreasonable in this respect. A promoter may also stipulate that publications planned by researchers should first be submitted to the promoter so that he can react to them within a

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66 Original version:

“Artikel 4

*In de overeenkomst mogen geen onredelijke beperkingen zijn opgenomen ten aanzien van de openbaarmaking van de resultaten van het onderzoek. Als onredelijke beperkingen worden in elk geval opgevat:*

- a. de voorwaarde dat openbaarmaking alleen is toegestaan na goedkeuring door de verrichter of uitvoerder;*
- b. een recht van de verrichter of uitvoerder om openbaarmaking door de ander te verbieden zonder opgaaf van redenen of onder opgaaf van redenen die niet opwegen tegen het belang van openbaarmaking van de gegevens;*
- c. een verbod op openbaarmaking van de gegevens of een deel daarvan onder de voorwaarde dat de voorgenomen openbaarmaking aan de andere partij moet worden voorgelegd, wanneer de termijn waarvoor dit verbod geldt meer dan negentig dagen is, behoudens bijzondere omstandigheden die een langere termijn kunnen rechtvaardigen;*
- d. een verbod op of beperkingen ten aanzien van openbaarmaking van de gegevens of delen daarvan dat voortduurt nadat twaalf maanden zijn verstreken na beëindiging van het onderzoek en publicatie van de resultaten is uitgebleven;*
- e. een alleenrecht op openbaarmaking van de verrichter of uitvoerder, tenzij dat in de gegeven omstandigheden als niet onredelijk moet worden beschouwd.”*

The distinction between ‘verrichter’ and ‘uitvoerder’ is defined in Article 1 of the Dutch act of 26 February 1998 on medical-scientific research on humans (*Wet houdende regelen inzake medisch-wetenschappelijk onderzoek met mensen, WMO*), as revised on 1 March 2006:

(*verrichter*) “f. the party accomplishing the scientific research: person, company, institution or organisation that takes responsibility for the launch, management or funding of the scientific research”, this corresponds to the definition of ‘promoter’ in the Belgian act of 7 May 2004 on human experimentation;

(*uitvoerder*) “g. the party carrying out the scientific research: doctor or person referred to in Article 3, e, in charge of carrying out the scientific research at a given site. If the actual carrying out of the research is entrusted to an employee or other auxiliary, the party uses this person is deemed to be the one carrying out the scientific research’, which corresponds to the definition of ‘investigator’ in the Belgian act of 7 May 2004 on human experimentation.

Original version:

*“f. degene die het wetenschappelijk onderzoek verricht: een persoon, bedrijf, instelling of organisatie die de verantwoordelijkheid op zich neemt voor het starten, het beheer of de financiering van het wetenschappelijk onderzoek;*

*g. degene die het wetenschappelijk onderzoek uitvoert: een arts of een in artikel 3, onder e, bedoelde persoon, die verantwoordelijk is voor de uitvoering van het wetenschappelijk onderzoek op een bepaalde locatie. Indien de feitelijke uitvoering geschiedt door een werknemer of een andere hulppersoon, wordt degene die van deze persoon gebruik maakt aangemerkt als degene die het onderzoek uitvoert.”*

reasonable period of time or has, for instance, had the opportunity to submit patent applications. It is important for the parties to succeed in resolving any differences of opinion together and for none of the parties concerned to have a veto.”

The Dutch CCMO thus expressly gives the medical-ethical assessment committees (METC) the task of checking whether research agreements contain unreasonable limitations on the publication of research findings.

Moreover, the same directive aims to limit the premature interruption of scientific research projects (Article 3) to the extent that, in the context of these projects, trial subjects have already been subjected to experimental interventions.

Or, to take the terms used by the CCMO in its 2010 annual report (p. 42): (free translation)

“The directive aims to monitor the interest of the publication of research findings and prevent the premature ending of research for non-medical-scientific reasons. In fact, in this case, the trial subjects included until then could have taken part in clinical research for nothing.”<sup>67</sup>

It may be concluded that the Netherlands are pioneers and are ahead of European initiatives and developments. Whereas the public was able to consult the basic data of research protocols relating to medical-scientific research (‘WMO’ act- *medisch-wetenschappelijk onderzoek*) from 2009 (<https://ToetsingOnline.ccmo.nl>), this possibility has only existed for research protocols included in the EudraCT database since 22 March 2011. It should also be pointed out in this context that the scope of application of the Dutch act is wider than that of European Directive 2001/20/EC, in which respect it is in line with the Belgian act. To date, no results have been included in the ToetsingOnline public register, but in the future, the CCMO does intend to record a summary. (See Annex 1, C.).

The CCMO thus aims to achieve transparency both for medical-scientific research and for its (ethical) assessment.<sup>68</sup>

### *Some conclusions*

The initiatives taken both by the Council of Europe and the Dutch CCMO show a trend towards granting medical ethics committees the power, when approving protocols, to assess the reasonable nature of the publication policy for research findings. The MECs should also be able to follow up the publication of research findings.

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67 Original version:

“De richtlijn beoogt het bewaken van het belang van openbaarmaking van de onderzoeksresultaten en het voorkomen van voortijdige beëindiging van onderzoek om niet-medisch-wetenschappelijke redenen. Dit kan immers tot gevolg hebben dat tot dan toe geïnccludeerde proefpersonen voor niets hebben deelgenomen aan een klinisch onderzoek.”

68 CCMO annual report 2010: summary p. 6.

## 3. GENERAL POINT OF VIEW AND RECOMMENDATIONS

### 3.1. Context

Publication bias or the underreporting of research findings – especially those that are negative – is a complex problem that involves various stakeholders.

Several initiatives have been developed over the past decade that aim to promote the transparency and hence the integrity of scientific research.

The public registers used for the prospective registration of protocols offer the possibility of following up the implementation of clinical trials and observing/researching the findings. The pharmaceutical industry is admittedly reluctant to communicate information from protocols concerning the early phases of research. This may, indeed, be information that is sensitive in terms of competition.

Adequate prospective registration in public registers alone is not enough to guarantee the transparency of scientific research. Research findings must also be made accessible. The pharmaceutical industry also supports transparency, while stressing the need to protect intellectual property rights, contract law, etc.

Here in Belgium, there are not as yet any public registers for the prospective registration of protocols. We should stress, however, that all interventional clinical studies with medicinal products have to be registered in the European EudraCT database before they begin. Since the start of 2011, some of the information from this database has been open for public consultation via the Clinical Trial Register or <https://www.clinicaltrialsregister.eu>. The research findings themselves are not yet included in the European database, but as a draft text from the European Commission reveals, the aim is indeed to register findings here as well in the future. In this respect, the European Medicines Agency (EMA) is following, with some delay, the initiatives taken by the American FDA which, since 2007, has registered all findings in the public register [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

As regards medical ethics committees, the Council of Europe guide (2010) for the members of research ethics committees, makes the following recommendations: once their research is complete, researchers must (1) forward a report or a synopsis of their conclusions to the medical ethics committee which initially assessed the research, and (2) confirm their initial proposals concerning the publication of findings in scientific journals or their public communication by other means. In order to thwart the publication of biased research findings, it is recommended that ethical approval by the ethical committees be made subject to prospective registration of the protocol in a public register. These committees should also always request that the research findings be made public.

In the Netherlands, the ‘Research contract assessment’ directive (*Richtlijn ‘Beoordeling onderzoekscontract’*) has been in force since 2009. According to this directive, the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek*, CCMO) gives medical-ethical assessment committees (METC) the tasks of checking whether protocols contain unreasonable restrictions as regards the publication of research findings.

In this context, the Advisory Committee on Bioethics first sets out its general point of view regarding the publication of research findings. This is followed by a number of recommendations in response to the actual request for an opinion which has been reformulated as follows:

When examining a protocol on human experimentation, can/must a medical ethics committee (MEC) check how the research findings – whether positive, negative or inconclusive – will be published or made publicly available?

## 3.2. General point of view regarding the publication of research findings

The Advisory Committee on Bioethics believes that as far as possible, the publication of all the findings of scientific research carried out on human subjects – whether they are positive, negative or inconclusive – is a matter of ethical duty.

By taking part voluntarily in an experiment, the subjects who agree to undergo this – both healthy volunteers and patients – in fact contribute to the development of scientific knowledge, which is to benefit the entire community. Whatever the origin (community and/or other promoters) of the resources used for scientific research on humans, the findings of human experimentation must be made publicly available, if only because the experimentation is carried out on humans. Moreover, when the community provides the research resources, it goes without saying that it is also entitled to the publication of the research findings. The choices and decisions made in terms of the health economy are also based on scientific findings. Distorting these findings can lead to less suitable strategic decisions and therefore have consequences, in particular in economic terms (inadequate funding, wastage, etc.), for society as a whole.

It should be pointed out here that the term ‘to make publicly available’ (‘openbaar maken’, ‘rendre public’) has a broader meaning than ‘to publish’ (‘publiceren’/‘publier’).

## 3.3. Recommendations

### a. Recommendation regarding the resources of medical ethics committees: a prior condition

In this context, the Committee refers to the comment it made in the introductory report relating to opinion No 13 of 9 July 2001 on human experimentation, point E, 4, c, end of paragraph 2: “real means (secretariat, staff) must be allocated to existing ethics committees and a training programme must be gradually developed.”

The Committee recalls its plea here. The possible development of the missions of medical ethics committees must be accompanied by greater professional support for these committees so that they can carry out their tasks properly. This is also a prior condition for the following recommendation.

### b. Recommendation on the ethical assessment and follow-up of protocols by medical ethics committees

The Advisory Committee on Bioethics recommends to the Belgian authorities, following the example of the Dutch Central Commission for research involving human subjects (*Centrale Commissie voor Mensgebonden Onderzoek*, CCMO), that medical ethics committees should be entrusted with the task of checking protocols with regard to the policy adopted for the publication of research findings. This means:

- that a protocol should contain clear information about the terms under which the research findings will be published or made publicly available;
- that the promoter should not be in a position to impose unreasonable restrictions as regards publication: promoters cannot ban or prevent the publication of negative findings; they cannot make their authorisation for publication mandatory, etc.

In order to safeguard the interests of the promoter, the Committee feels it is acceptable for latter to be able to request the observance of a reasonable period – of about one year – between the moment when the findings of the research become available and the time they are published.



The Advisory Committee on Bioethics recommends expressly entrusting the medical ethics committees with the task of following the protocols for which they have issued a positive opinion until the findings are published.

c. Recommendation in the context of the possible revision of European Directive 2001/20/EC

The problem of the publication of **all** research findings is complex and requires an approach that goes beyond the limits of Belgian territory. The Committee therefore recommends to the Belgian authorities that this problem should be considered at European level. In the context of the current assessment/revision of European Directive 2001/20/CE relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, the Advisory Committee on Bioethics believes that it is advisable to hold a debate on this issue.

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**Annexes 1 to 4 of the opinion are included in a separate document**

The opinion was prepared in the select commission 2010/1, consisting of:

Joint chairpersons	Reporter	Members	Member of the Bureau
Marc Bogaert	Marc Bogaert	Mylène Baum	Paul Schotsmans
Andre Herchuelz		Paul Cosyns	
		Patrick Cras	
		Yvonne Denier	
		Martin Hiele	
		Guy Lebeer	
		Jean-Marie Maloteaux	
		Marie-Geneviève Pinsart	
		Robert Rubens	

#### Member of the secretariat

Veerle Weltens

The working documents of the select commission 2010/1 – request for opinion, personal contributions of the members, minutes of the meetings, documents consulted – are stores as Annexes 2010/1 at the Committee’s documentation centre, where they may be consulted and copied.

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This opinion is available at [www.health.belgium.be/bioeth](http://www.health.belgium.be/bioeth), under the heading “opinions”.