

**“THE WORLD MEDICAL ASSOCIATION’S  
DECLARATION OF HELSINKI:  
HISTORICAL AND CONTEMPORARY PERSPECTIVES”**

by

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**The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.**

*—Para. 1 of the October 2000 version  
of the Declaration (Helsinki VI)*

## I. What is the Declaration of Helsinki?

Writing in the *British Medical Journal* just after the adoption, by the 52<sup>nd</sup> General Assembly of the World Medical Association (WMA) meeting in Edinburgh on 3-7 October 2000, of the sixth version of the WMA's Declaration of Helsinki (originally adopted in 1964),<sup>1</sup> Christie refers to the document as having become "the most widely accepted guidance worldwide on medical research involving human subjects."<sup>2</sup> It has also been described as "the cornerstone of biomedical research for the last 30 years [and] the largely unquestioned anchor for ethical decision-making in clinical trials" (Crawley and Hoet<sup>3</sup>), while two German experts have stated that: "...though [the Declaration] is not a legally binding instrument under international law [its] influence on medical ethics and national regulations on biomedical research cannot be overstated" (Deutsch and Taupits<sup>4</sup>).

Quite apart from these and numerous other observations on the importance of the Declaration, innumerable examples could be cited of the considerable extent to which the Declaration – or major sections thereof – have been incorporated or embodied in other international and national instruments, guidelines, laws, regulations, and other non-binding texts on human subjects research. For example, in a 9-year-old instrument applicable to human reproduction research in the Islamic world, specific reference is made to the 1964 and 1975 versions of the Declaration of Helsinki, as being among the "ethical requirements and rules" governing such research.<sup>5</sup>

An editorial published in the *Lancet* just one week before the revision of the Declaration was adopted in Edinburgh quotes a provision of the revised text to the effect that the "design and results of medical research studies should be made publicly available" – and then goes to the assert that the revision process "should be similarly transparent."<sup>6</sup> One of the purposes of this paper is precisely to describe that process, the outcome thereof, and more generally the impact of successive versions of the

Declaration, and the ongoing debate on some of the key provisions of Helsinki VI, i.e. the version adopted unanimously at the Edinburgh General Assembly of the WMA.

It may be appropriate at this juncture to affirm that the Declaration is widely perceived as both a set of ethical precepts and as a guide to the protection of human rights in human experimentation. Thus, writing in the Foreword to the Guidelines on Ethics for Medical Research issued in 1993 by the South African Medical Research Council, Benatar affirms that the “1964 Declaration of Helsinki (latest revision 1989) and the 1966 International Covenant on Civil and Political Rights... express society’s fundamental concern for the protection of the rights and welfare of all human subjects of human experimentation.”<sup>7</sup> The relationship between the ethical aspects of human experimentation and human rights has been amply explored, notably by Katz<sup>8</sup> and, more recently, by Andreopoulos (with particular reference to international human rights law).<sup>9</sup> The Declaration is reproduced and/or commented on in classic contributions to the bioethics literature on human subjects research,<sup>10-15</sup> including major reference works,<sup>16</sup> as well as major publications that address the interface between health (including biomedical research) and human rights.<sup>17, 18, 19</sup>

It should be mentioned that journal publishers often specify that biomedical research published in their respective journals must have complied with (*inter alia*) the Declaration. Thus, in the case of WHO, it is stated in the Guidelines for Contributors to the WHO Bulletin that “WHO publishes the results of research involving human subjects only if such research has been conducted in full accordance with ethical principles, including the provisions of the World Medical Association Declaration of Helsinki (as amended by the 52<sup>nd</sup> General Assembly, Edinburgh, Scotland, October 2000) and the additional requirements, if any, of the country in which the research was carried out....”<sup>20</sup>

There are corresponding (though somewhat dated) provisions in the fifth edition (1997) of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee of Medical Journal Editors (the so-called Vancouver Group); contributors to the more than 500 journals that accept these Requirements are asked to “indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.’<sup>21</sup>

## II. A historical overview: the development of the Declaration of Helsinki

It is noteworthy to point out that prior to the Second World War, no international statement of the ethical precepts that should govern human experimentation had been adopted nor, does it seem, had any international entity discussed the subject. National legislation was very limited, and it appears that the only texts on the subject were a Directive issued on 29 December 1900 by the Prussian Minister of Religious, Educational and Medical Affairs, the Circular of 28 February 1931 of the (German) Reich Minister of the Interior issuing Guidelines on Innovative Therapy and Scientific Experimentation<sup>19</sup> and a Resolution of 23 April 1936 of the Bureau of the Medico-Scientific Council of the People’s Commissariat for Health of the Russian Soviet Federated Socialist Republic, part of the then Soviet Union.<sup>22</sup> The paucity of laws, regulations or guidelines is perhaps surprising, given the substantial amount of medical experimentation being carried out at the time.<sup>23</sup> In this connection it should be mentioned that Katz<sup>24</sup> reports that in 1916, “the Harvard physician Walter Cannon recommended to the House of Delegates of the American Medical Association that it endorse the importance of obtaining patient consent and cooperation in human experimentation. His proposal, however, was not brought up for consideration. One influential physician observed, ‘it would open the way for a discussion of the importance of obtaining the consent of the patient before any investigations are carried on which are not primarily for the welfare of the patient.’ ”

The literature on the 1946-1947 Doctors’ Trial (the so-called “Medical Case”) at Nuremberg is abundant,<sup>14,19,24,25</sup> and there have been numerous efforts to trace the linkages between the Nuremberg Code and the first, 1964 version of the Declaration,<sup>26</sup> as well as subsequent versions, and other international guidelines or the equivalent on the ethics of human experimentation.<sup>10</sup> We propose to concentrate here briefly on the sequence of events which led from Nuremberg to Helsinki, relying both on published and unpublished sources,<sup>27</sup> including the WMA’s own Summary History of the Declaration,<sup>28</sup> and a paper by one of us (SSF) originally presented at a Workshop in London.<sup>29</sup> It should be noted at this juncture that the WMA was established in London

in 1946, while the First Annual Meeting of its General Assembly was held in Paris in September 1947. On that occasion, a number of the provisions of resolutions adopted by the Assembly alluded to crimes committed since 1933 by certain members of the medical profession in Germany during World War II. However, it was not until 1953 that the idea of a position paper on human experimentation was first discussed by the WMA's Medical Ethics Committee. In the following year, a "Resolution on Human Experimentation: Principles for Those in Research and Experimentation" was adopted by the 8<sup>th</sup> General Assembly of the WMA, held in Rome on 26 September - 1 October 1954. There are five Principles of which the headings are as follows: I. Scientific and moral aspects of experimentation; II. Prudence and discretion in the publication of the first results of experimentation; III. Experimentation on healthy subjects; IV. Experimentation on sick subjects; and V. Necessity of informing the person who submits to experimentation of the nature of the experimentation, the reasons for the experiment and the risks involved.

This resolution was influential in the formulation of a 1955 guidance document on research on humans in the Netherlands<sup>30</sup> and, no doubt, in other countries whose national medical associations were members of the WMA at the time. Further research is needed to explore this particular aspect, which may be of some historical interest.

Other key stages in the development of Helsinki I have been described in the literature<sup>26</sup> and it would be duplicative to describe them in any detail. Suffice it to say that they included the following:

- Publication in March 1960 of a fairly extensive section on human experimentation (including a contribution by Henry Beecher) in the *World Medical Journal* (the WMA's "house journal");
- Draft Code of Ethics on Human Experimentation formulated in 1961 by the WMA's Medical Ethics Committee (chaired by the then Editor of the *British Medical Journal*, Dr Hugh Clegg);
- Report on this subject presented by Clegg to the 15<sup>th</sup> WMA General Assembly (Rio de Janeiro, 15-20 September 1961);

- Draft Code of Ethics on Human Experimentation<sup>31</sup> published in 1962 in the *British Medical Journal*;
- Draft of the Code discussed by the 44<sup>th</sup> Session of the WMA Council (Chicago, 6-12 May 1962);
- Further discussions on the draft by various Sessions of the Medical Ethics Committee and the Council;
- Final version of the Declaration adopted by the 18<sup>th</sup> World Medical Assembly (Helsinki, 13-14 June 1964);
- Publication of the Declaration in the September 1964 issue of the WMA's journal.<sup>32</sup>

It would, even today, be of interest to review each of the successive revisions and the commentaries thereon. Suffice it to say that some of the amendments were of major substantive importance, such as the introduction of committee review (in Helsinki II, adopted in 1975) and the introduction of provisions on the use of inert placebos (in Helsinki V, adopted in 1996). We shall not dwell on those other modifications, however important, since there is already an abundant literature on them. Later in this paper we shall focus on the events that led to the Edinburgh revision, and some of the relevant literature.

### **III. THE IMPACT OF THE DECLARATION ON INTERNATIONAL AND NATIONAL LEGAL INSTRUMENTS AND OTHER MEASURES**

The 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, developed by CIOMS in close cooperation with WHO,<sup>33</sup> discuss in a section entitled "International Declaration and Guidelines" the nature of the Nuremberg Code and the background to Article 7 of the 1966 International Covenant on Civil and Political Rights (which prescribes that "... no one shall be subjected without his free consent to medical or scientific experimentation") and then goes on to affirm that the "Declaration of Helsinki... is the fundamental document in the field of ethics in biomedical research and has had considerable influence on the formulation of international, regional and national legislation and codes of conduct." The current CIOMS Guidelines themselves (now under revision) supersede a 1982 text, the

objective of which was to “indicate how the fundamental ethical principles... as set forth in the Declaration of Helsinki, could be applied effectively, particularly in developing countries, taking into account culture, socioeconomic circumstances, national laws, and executive and administrative arrangements.”

In this Section we shall demonstrate the considerable extent to which the Declaration has been endorsed, implicitly or explicitly, as one of the cornerstones of other instruments. For example, the 1995 WHO Guidelines for GCP for trials on pharmaceutical products include an affirmation (in para. 3.1) that the current revision of the Declaration of Helsinki is the “accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials.”<sup>34</sup> The 1996 Harmonised Tripartite Guideline for GCP, developed by the (European Union/Japan/USA) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),<sup>35</sup> states (in para. 2.1) that “Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.” The Declaration is referred to as a basic reference text (to be consulted in HIV vaccine development activities) in the May 2000 UNAIDS Guidance Document on Ethical Considerations in HIV Preventive Vaccine Research.<sup>36</sup> The new European Union Directive on GCP for clinical trials (2001/20/EC), which was published on 1 May 2001, includes a preambular paragraph 2 affirming that “The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration.”<sup>37</sup>

The Commonwealth Medical Association’s 1993 Guiding Principles on Medical Ethics<sup>38</sup> include a Principle 16 (Medical Research), stating that the provisions of the Declaration should be observed, and there are corresponding provisions in the 1989 Nordic Guidelines on “Good Clinical Trial Practice”<sup>39</sup> and in the current version of the PAHO (Pan American Health Organization) Ethical Guidelines for Research Involving Human Subjects.<sup>40</sup>

It would be a formidable task to detail the national laws, regulations, and guidelines or the equivalent and we propose to cite here merely a few, not necessarily

representative, examples, selected from materials available to the WMA and, in the main, issued or updated in the last few years. Both developing and developed countries' instruments are covered and citations are in many cases not given since to do so would extend the list of references to excessive proportions.

The *Australian* National Statement on Ethical Conduct in Research Involving Humans, issued in 1999,<sup>41</sup> includes a provision to the effect that before granting approval to a clinical trial, a Human Research Ethics Committee must be satisfied that the protocol conforms to, *inter alia*, the Declaration of Helsinki. According to Delfosse,<sup>42</sup> *Belgian* legislation is required to conform to the Declaration, while a US report indicates that in *Brazil*, existing legislation (1996-1999) lays down that research protocols must comply with the requirements of the Declaration.

The *Chinese* Clinical Trial Administration Norms, issued on 1 September 1999 by the Director of the National Drug Regulation Administration,<sup>43</sup> prescribe that all "research involving human subjects must comply with the ethical principles in the Helsinki Declaration and [the 1993 CIOMS Guidelines], i.e. justice, respect, maximum benefits to human subjects, and avoidance of harms as far as possible." There are also Guidelines on this subject issued in 1998 by the Ministry of Health.<sup>44</sup>

There is no explicit reference to the Declaration of Helsinki in existing national legislation in *Germany* on clinical trials of pharmaceutical and medicinal products. However, reference is made to the Tokyo revision of the Declaration (Helsinki II) in the official background text to Sections 40 and 41 of the *Arzneimittelgesetz* (the Medicines Law). Moreover, the individual regional Chambers of Physicians are empowered to issue Professional Codes. There are being harmonized on the basis of the so-called "Specimen Professional Code of the Federal Chamber of Physicians", in the version adopted by a decision of the 100<sup>th</sup> German Physicians' Assembly, held in Eisenach in 1997. Section 15 (Research) of this model Code lays down that the 1996 version of the Declaration of Helsinki (Helsinki V) is to underlie the deliberations of ethics committees reviewing biomedical research projects involving humans.

The Ethical Guidelines for Biomedical Research on Human Subjects, issued in 2000 by the *Indian* Council of Medical Research, refer specifically to the Declaration in one

of the introductory rubrics of the “Statement of General Principles in Biomedical Research Involving Human Subjects.”<sup>45</sup>

*Israel* is one of the few examples of which we are aware in which the Declaration as such (1975 version, i.e. Helsinki II) is incorporated in the relevant legislation, viz. the Public Health (Medical Experiments Involving Human Beings) Regulations, 1980, as last amended in 1999. The ethical review committees in the country are known as “Helsinki Committees” – a perhaps unique tribute to the importance of the Declaration.

In *Japan*, Ordinance No. 28 of 27 March 1997 of the Ministry of Health and Welfare on the standards for the conduct of clinical trials of pharmaceutical products includes a Sec. 2 (1) prescribing that clinical trials should be performed in accordance with ethical principles based on the Declaration of Helsinki and the standards laid down in the Ordinance.

In *New Zealand*, Document 3 (Research Involving Humans or Human Materials) of the October 1997 Health Research Guidelines on Ethics in Health Research include a major Section C (Declaration of Helsinki – Principles of Medical Research on Human Subjects). This sets out a series of nine guiding principles for clinical investigators, “based on the Declaration of Helsinki statements”.<sup>46</sup>

In *Norway*, the terms of Reference for each of the five Regional Medical Research Ethics Committees, issued by the Ministry of Education, Research and Church Affairs on 19 January 1989 and last amended on 5 March 1999, prescribe that such committees are to “give advice and guidance based on generally accepted principles of research ethics with due attention to guidelines established by national or international bodies (e.g. the Declaration of Helsinki).”

The Good Practices for Clinical Trials (BEPC in French) appended to the Regulations of 18 November 1993 on medicines at the clinical trial stage, issued by the Intercantonal Office for the Control of Medicines (OICM/IKS) of *Switzerland*, indicate that they are based on the most recent version of, *inter alia*, the Declaration of Helsinki. It is stated in para 1.1 that the “most recent version of the Declaration of Helsinki constitutes the ethical basis of clinical trials. It must be fully known to, and complied

with by, any person involved in a research activity on man” (informal translation from French).

We may cite *Uganda* as an example of a developing country in Africa. Its 1997 Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda states that "certain protections derive from the provisions of the Nuremberg Code and the Helsinki Declaration...". The 1993 *South African* Guidelines on Ethics for Medical Research, which are particularly comprehensive and detailed, reference the Declaration.<sup>7</sup>

As far as the *United Kingdom* is concerned, the Medical Research Council's March 1998 Guidelines for Good Clinical Practice in Clinical Trials includes a section (5.3.1) stating that the "current revision of the Declaration of Helsinki... is the accepted basis for clinical trials ethics and must be known and implemented by those engaged in research involving human participants." In 1999, the MRC issued Interim Guidelines on "Research Involving Human Participants in Developing Societies: Ethical Guidelines for MRC-sponsored Studies." An introductory paragraph states that the "MRC's key principles, which are underpinned by the Declaration of Helsinki... apply to research conducted in developing societies." In its Guidelines on ethics committees, updated as of August 1996, the Royal College of Physicians of London states that "research investigations on human beings should conform with codes such as those of the World Medical Association Declaration of Helsinki in its current revision..."<sup>47</sup> The Guidelines for the Ethical Conduct of Medical Research Involving Children, published in February 2000,<sup>48</sup> are based on several earlier documents, including Helsinki V (1996); these Guidelines were developed under the auspices of the Royal College of Paediatrics and Child Health.

In the *United States*, Part 46 (Protection of Human Subjects) of Title 45 (Public Welfare) of the Code of Federal Regulations includes a Subpart A (Federal Policy for the Protection of Human Subjects (Basic [Department of Health and Human Services] Policy for Protection of Human Research Subjects). This so-called "Common Rule", in the current version dated 18 June 1991, prescribes in Sec. 46.101 (To what does this policy apply?) that when "research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human

subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Association Declaration of Helsinki (amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized).” Title 21 (Food and Drugs) includes a Part 312 (Investigational New Drug Application [IND]); Sec. 312.120 (Foreign clinical studies not conducted under an IND) lays down, in para. (c) (1), that “Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the “Declaration of Helsinki”... or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.” The full text of Helsinki IV (1989 version) is reproduced in this Part.

Much additional information on the “reception” of the Declaration at the national level is provided in a recent paper by Herranz.<sup>49</sup>

#### **IV. THE IMPACT OF THE DECLARATION ON SOCIETY**

Some of the wisest words on this critically important aspect have been written by Justice M.N. Venkatchaliah, a former Chief Justice of India, in his Foreword to the 2000 Indian Guidelines referred to above: “Genome-mapping, Genetic Recombinant Engineering, Assisted Reproductive technology, Stem-Cell Research, Human cloning, etc. have opened up hitherto unimagined vistas in the practical application of Biomedical Technologies for the benefit of the mankind. Biomedical Research is perched on the threshold of a bold and brave new world. Crucial to its management is the ability of the scientists and the society to handle these forces of change. Correspondingly, as in all frontier-line researches, our ignorance of the areas of the yet unknown might, paradoxically, expand with the expansion of our knowledge. Biomedical Research has acquired dimensions which are at once exciting and awesome. It raises some delicate and difficult issues of ethics which need to be [addressed] with sensitivity to human values and with great circumspection. While research which promises to mankind the great blessings of Science should not be stifled by too restrictive an approach, however, great care should be taken to ensure that something does not go out of hand. Therefore, any system of ethical guidelines on research needs to be cognizant of, and informed by, a sensitive balance of the risks and benefits.”

Also relevant in this context are the introductory sections of many of the international and national instruments on human subjects research referred to above, notably the Preamble to the 1999 Australian National Statement on Ethical Conduct in Research Involving Humans. It is stated that "Ethics and ethical principles extend to all spheres of human activity. They apply to our dealings with each other, with animals and the environment. They should govern our interactions not only in conducting research but also in commerce, employment and politics. Ethics serve to identify good, desirable or acceptable conduct and provide reasons for those conclusions."

In addressing the purpose of the Statement, it is stated that "it identifies the ethical principles and values which should govern research involving humans. Throughout this Statement the term 'involving' is used to mean not only those who are the principal focus of the research but also those on whom the research impacts. It provides guidance for researchers, ethics committees, institutions, organisations and the public on how such research should be designed and conducted so as to conform to those principles and reflect those values." In discussing the historical context of the Statement, reference is made to only two international instruments, namely the Nuremberg Code and the Declaration of Helsinki.

Society has a clear interest in the implementation of the Declaration not least because the history of human experimentation cannot be recounted without reference to the abuses described, for example, in the writings of Beecher (USA)<sup>50</sup> and Pappworth (UK)<sup>51</sup> and, more recently, in an important US Report.<sup>52</sup>

In a recent Canadian Report, it is affirmed that the ethics of health research has three main objectives, namely, 1. The *promotion* of socially beneficial research; 2. *Respect* for the dignity and rights of research subjects; and 3. As an overarching aim, the maintenance of *trust* between the research community and society as a whole (emphasis in the original).<sup>53</sup> The community of physicians and other medical researchers will find much of value in this Report, which was commissioned by the Law Commission of Canada. In his Preface, the Principal Investigator, Michael McDonald, makes the point – on behalf of the research team – that "while we all knew beforehand that research ethics was not simply a matter of codes and policy statements, we were surprised to see

how substantial the gaps were between the ideals expressed in policy and the ground arrangements for accountability, effectiveness and other criteria for good governance.” It should be mentioned that this Report includes a substantial Section G-1, “Biomedical research ethics: convergence and divergence of national and international standards”; the international standards examined are Helsinki V, the CIOMS Guidelines, the ICH Guideline and the Council of Europe’s 1997 Convention on Human Rights and Biomedicine (in that order). The Canadian authors’ visionary approach, and recognition of society’s interest in the benefits of medical and, more generally, health research, are eloquently expressed in a rubric entitled “General Conclusion”: “We urge a return to the fundamental concerns that motivate health research involving human subjects – the desire for socially beneficial research and the concern for the protection of human subjects. It is our conviction that these cannot be posed as an “either-or” choice. It is a “both-and” choice. Our society needs both socially beneficial research and the protection of human subjects. Without these together, there is the serious risk of undermining the fundamental trust relations underwriting health research – the public’s trust in researchers, research institutions and sponsors and more specifically, the trust of research subjects whose continuing participation in research is essential not only to health but also to health care. Governance is about maintaining, enhancing and, where necessary, restoring trust in transparent, accountable and effective ways...”.

Protection of human subjects, without prejudice to the conduct of medical research and the broad interests of society in the advancement of clinical medical sciences, is precisely the goal of the WMA’s Declaration, which has been referred to by a Past President of the Association, Dr Daniel Johnson, as the “crown jewel” of the WMA.<sup>54</sup>

## **V. THE REVISION PROCESS, 1998-2000**

The initial impulse for a revision of the 1996 version came from the American Medical Association.<sup>55</sup> A revised version was prepared and duly issued as a WMA document (17.C/Rev1/99) and subsequently published.<sup>56</sup> It was discussed by the WMA Council at its 153<sup>rd</sup> Session in Santiago, Chile in April 1999. The proposed revision aroused considerable debate and controversy (see below) but while this debate was underway, the WMA itself was carefully monitoring and, from time to time, discussing key issues and strategy matters. Thus, in an article published at the beginning of 1999 in

its own journal,<sup>57</sup> a summary was presented of the WMA's expectations regarding the Declaration, and it was indicated that a decision had been taken to preserve the existing text as much as possible. One contributor to the discussions (R.J. Levine) expressed his desire to maintain it as a "concise formal document" which, he noted, has been referred to as "having an air of majesty to it". Later the same year, the same journal presented the WMA's proposed timetable for the revision process between October 1999 and October 2000, as well as a series of recommendations of the WMA's Workgroup on the Revision of the Declaration of Helsinki.<sup>58</sup> One of the recommendations was that the views of a wide range of experts, as well as of the public at large, should be sought on the new draft that had been submitted by the Workgroup. This was duly accomplished using the WMA website; in addition, the views of all National Medical Associations belonging to the WMA were sought.

The debate concerning the revision was very animated and many controversial points were covered by the numerous biomedical scientists, ethicists, lawyers, and others who made contributions. Perhaps the earliest international meeting to discuss the revision was the International Symposium on Freedom and Control of Biomedical Research – Planned Revision of the Declaration of Helsinki, held in Göttingen, Germany on 7-10 April 1999 under the joint auspices of institutes at three German Universities (Göttingen, Heidelberg and Mannheim). A series of 20 Recommendations were adopted, one of which was that the "Declaration should continue to limit itself to the short and clear statement of the fundamental principles of medical research".<sup>59</sup>

In August 1999, a Symposium on the WMA's proposed changes to the Declaration was held in Melbourne and a report thereon has been published by Spriggs.<sup>60</sup> Numerous substantive points in what was then the proposed revised text were discussed and two resolutions on procedural matters were adopted.

One month later, a major Workshop on "Revising the Declaration of Helsinki: A Fresh Start" was held in London under the joint auspices of the *Bulletin of Medical Ethics* and the Brussels-based European Forum for Good Clinical Practice. A special issue of the *Bulletin* (N° 150) was published, containing (*inter alia*) the 1964, 1975 and 1996 versions of the Declaration and what was then the draft revised version (i.e. the version that had been discussed by the WMA's Medical Ethics Committee at its April

1999 meeting in Santiago). The issue likewise includes the so-called “Göttingen paper”, i.e. the conclusions of the April 1999 Symposium referred to above, as well as exhaustively referenced papers by Troyen Brennan and Robert Levine that had previously appeared in the *New England Journal of Medicine*.<sup>61,62</sup> It would extend the length of this paper to excessive proportions to replicate the arguments set forth in these two papers, but it may be apposite to cite the concluding paragraph of Brennan’s paper, since it appears to embody the philosophy that guided the WMA in the final stages of the overall revision process: “It is time for us to step back and reexamine the ethical foundation of human research. The principles exemplified by the current Declaration of Helsinki represent a delicate compromise that we would modify only after careful deliberation. The declaration has served us well, protecting vulnerable populations yet allowing research to proceed. Human subjects committees rely on it heavily, more so today than before, as they examine increasingly difficult ethical issues in the conduct of studies involving human subjects.”

A report on the Workshop was published in the *Bulletin of Medical Ethics* in October 1999.<sup>63,64</sup> The report is particularly helpful as it discusses, in lucid and cogent terms, the aims of the Workshop, the participant’s backgrounds, the topics of discussions, specific paragraphs of the Declaration that were considered, one area on which there was consensus (namely, the need to involve a “wide group of stakeholders” in the revision process), suggestions for revision, possible ways forward and overall conclusions. Three major points in the discussion were:

- whether the distinction between therapeutic and non-therapeutic research in the Declaration is needed;
- what standard of care is ethically required for participants in biomedical research; and
- the use of placebos in biomedical research.

No clear consensus was reached in these areas, which also received major attention in the abundant literature that was published in many journals during the revision process.

On 8 February 2000, a “National Forum on the Declaration of Helsinki: Brazilian Perspective” was convened at the offices of the Federal Board of Medicine in Brasilia. The Forum reached consensus on eight points, contained in what is termed the “Letter from Brasilia”, the first two of which read as follows:

- “1. The Declaration of Helsinki should be maintained as an overall set of concise principles.
2. Even though the Declaration of Helsinki is the responsibility of the World Medical Association, the document should be considered the property of all humanity.”

Reference should also be made to a Seminar on ethical issues in international health research, held in Kwazulu, Natal, South Africa, in July 2000; a report on this meeting has been published by Eckstein,<sup>65</sup> who notes that in his Opening Address Benatar made the point that while the “ability to do good science gets better and better, little effort has been made in attaining ethical excellence”. Particular attention during the discussions at this Seminar was focussed on the issues of equitable access to health research, ethical guidelines, the notion of standard of care, the role and limitations of institutional review boards, and informed consent.

The debate on the Declaration, and on its proposed revision, was extensive and was reflected in contributions (including editorials and letters) to several pre-eminent medical and bioethics journals. In particular, the papers by Brennan and Levine cited above elicited numerous comments and varying standpoints<sup>66-76</sup> and in general there was an abundant – and enriching – debate on the issues (and procedures) involved.

By the time of the WMA Council’s session held in Divonne-les-Bains, France, in May 2000, a revised version of the Declaration has been prepared and approved as a “working document” and this was then circulated to all Member Associations and posted on the WMA website ([www.wma.net](http://www.wma.net)). Particular reference must be made to the three-member Workgroup (originally established during the Council’s session of April 1999). This Workgroup met in Helsinki in August 2000 and, by October of the same year, had reached consensus on a text that incorporated, as far as possible, the various proposals and suggestions that had been formulated during the consultation process, not least by members of the public as well as by Member Associations. In the Council’s

report to the 52<sup>nd</sup> General Assembly in Edinburgh, it was stated that the revision process had probably been the most far-reaching of any such process in the WMA's history. Literally hundreds of comments had been received from the different stakeholders in biomedical research.

Finally, first the Council and then the plenary of the General Assembly endorsed (on 7 October 2000) the revised Declaration and thereby concluded what had been a quite unprecedented process in the history of international research ethics.

## **VI. MAJOR CHANGES IN THE OCTOBER 2000 VERSION OF THE DECLARATION**

The new version of the Declaration was published very soon after its adoption in a journal widely read by persons interested in research ethics,<sup>77</sup> the text being followed by a paragraph-by-paragraph enumeration of the changes – both major and minor – introduced. It would be duplicative to list these changes here. In the view of the Editor of the *Bulletin of Medical Ethics*, para. 30 is “potentially the most far-reaching of all the changes to the Declaration”. It requires “study patients to have access after the study to the best treatment identified by the study”. A particularly noteworthy provision (para. 29) is stated to maintain “the requirement that best current treatment be the comparator in clinical trials”; placebos may “only be used where no proven method exists”. There is a “substantially expanded” paragraph (32) on “how to undertake innovative therapy, and on the need to “turn it into formal research whenever possible”.

Only a few weeks were to elapse before a major scientific journal published a detailed account of some of the key elements of the new version, focussing particularly on contentious issues (such as the use of placebo-controlled trials).<sup>78</sup> Other commentaries on the new version appeared elsewhere,<sup>79-82</sup> focussing on particular aspects of the new version, and it may be anticipated that there will be further contributions in the coming months on the issues under discussion, not least in the light of other guidance documents on ethical issues in medical research likely to be finalized in the foreseeable future.

In his capacity as Secretary General of the WMA, one of us (DH) submitted a report on the implementation of the new version of the Declaration to the 159<sup>th</sup> Session of the WMA Council.<sup>83</sup> This summarized the revision process and the overall reaction to the new text, which had been extremely positive. It also acknowledged the criticisms that had been levelled in respect of specific provisions of the text, notably paragraphs 29 and 30. These had led, it was stated, to a “rather worrying practice by major regulatory agencies such as the [US Food and Drug Administration] and the [European Union] drug regulatory bodies to disregard the latest revision.” The document went on to enumerate negative reaction to the revised Declaration, with a distinction being made between primary and secondary issues. In the light of this situation, the Council agreed to set up a working group to examine the concerns that had been expressed and to interact with other bodies to harmonize guidelines that have been or are in the course of being formulated. Annex 1 to the above-mentioned document presents a text that was agreed upon at a conference held at the end of March 2001 in Pretoria. A summary of the outcome of the conference has already been published as has a statement reflecting the views of the US Government of the new version.<sup>84</sup> This statement focuses on varying interpretations of paras. 29 and 30 as well as on the types of research to which the Declaration may not be applicable.

## **VII. COMMENTARY ON THE OCTOBER 2000 VERSION OF THE DECLARATION**

Given the controversy that has surrounded the new version of the Declaration, as has been illustrated above, it is clear that a further revision or explanatory statement might well be appropriate; this is a matter that the working referred to be one of us (DH) in a presentation at the May 2001 session of the WMA Council will have to discuss.<sup>83</sup> This debate will hopefully be illuminated by a statement to the *BMJ* correspondent on the occasion of that session:

“We are anxious to ensure that no good ethical research is restricted, while at the same time we are adamant not to compromise the ethical principles the medical profession stands for.”<sup>85</sup>

Any new version will no doubt be formulated in the light of the deliberations of, and recommendations adopted by, the US National Bioethics Advisory Commission<sup>86</sup> and, in the United Kingdom, the Nuffield Council on Bioethics Working Party on Healthcare-Related Research in Developing Countries. It will also have to take into account a Position Statement adopted by the European Agency for the Evaluation of Medicinal Products/Committee for Proprietary Medicinal Products, meeting in London on 28 June 2001, on “The Use of Placebo in Clinical Trials With Regard to the Revised Declaration of Helsinki”.<sup>87</sup> The Statement refers to the October 2000 version of the Declaration, affirming that “it remains a vital expression of medical ethics whose aims deserve unanimous support”.

However, it takes issue with the provisions of the Declaration dealing with the use of placebos (para. 29). The concluding paragraph of the statement reads as follows:

“Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products. Reliable scientific evidence of efficacy and safety ensures that a reliable evaluation of the balance of benefits and risks for a particular medicinal product can be made, avoiding erroneous decisions of either withholding or mistakenly granting a marketing authorisation. Provided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP and the EMEA that continued availability of placebo-controlled trials is necessary to satisfy public health needs.”

The statement does acknowledge that unethical “abuses of placebo in trials of medicinal products may occur in any country, and this potential for abuse should be eliminated. Similar ethical standards should be applied in trials performed in the European Union as well as in foreign countries. These aspects fall within the responsibilities of Ethics Committees reviewing protocols of clinical trials; they are also emphasized in ICH E6 guideline on Good Clinical Practice and in the recent Council Directive 2001/20/EC on Good Clinical Practice”.

## VIII. RELATIONSHIP WITH OTHER GUIDELINES ON RESEARCH ETHICS

We have already referred to the impact of the Declaration on other international codes, etc. (p. 6) and its relationship with other instruments. In a sense, the Declaration constitutes a framework of principles which are then embodied and expressed in more concrete (and often rather detailed) terms in, for example, the 1993 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, a document which was prepared in close cooperation with WHO. These Guidelines are currently in the course of revision in the light of developments in research ethics (notably issues and controversies that have arisen in HIV/AIDS research, e.g. in perinatal HIV transmission prevention trials, during the last few years).<sup>69</sup> Every effort is being made to ensure maximum harmonisation between the revised Guidelines (the process is likely to terminate at the end of 2001 or early 2002) and the October 2000 version of the Declaration of Helsinki.

The relationship between the Nuremberg Code and the Declaration of Helsinki has been the subject of a voluminous literature<sup>19</sup> and need not be discussed here. Suffice it to say that the Nuremberg Code was formulated by a Military Tribunal made up of US judges at the termination of an unprecedented trial – the so-called “Doctors’ Trial” (also known as the “Medical Case”) of Nazi physicians who had performed wholly reprehensible medical experiments on concentration camp prisoners during World War II. No consent was sought or obtained and thus it is not surprising that the Code places such emphasis on the voluntary consent of subjects of medical experimentation. As Dickens has pointed out, the “historic Nuremberg Code of 1947, which the 1964 Declaration of Helsinki was developed to amplify and explicate outside the Code’s conditioning environment of outrageous crimes against humanity, states as its first principle that: The voluntary consent of the human subject is absolutely essential... The Code makes no mention of elements that are also considered critical to the ethical planning and conduct of research with human subjects, such as independent ethical review and, for instance, due preservation of confidentiality and disclosure of its limits. The Declaration of Helsinki considerably advances the detail of ethical conduct in research. Further, it addresses research with subjects incapable of making their own decisions or consent, reflecting the recognition that research extends beyond the exploitive sacrifice of vulnerable subjects that framed the Nuremberg Code, to include

research, such as with mentally disabled people and with infants and children, that it is ethical to undertake and may be unethically discriminatory to deny.”<sup>88</sup>

The relevance of the Declaration to current international guidelines for Good Clinical Practice (GCP) is graphically illustrated by its inclusion (as an Annex) to the 1995 WHO GCP for trials on pharmaceutical practice and (as an Appendix) to the 1996 ICH Harmonised Tripartite Guideline for GCP; the only other document so appended in the case of the ICH Guideline is the well-known Belmont Report, i.e. the April 1979 Report on “Ethical Principles and Guidelines for the Protection of Human Subjects of Research”, formulated by the (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

At this juncture reference should be made to the normative work of the Council of Europe on biomedical research. On 6 February 1990, the Committee of Ministers of that Strasbourg-based body (which now has 43 Member States) adopted a Recommendation (N° R (90) 34) to Member States concerning medical research on human beings. Reference is made to the 1989 version of the Declaration of Helsinki in one of the preambular paragraphs. Perhaps surprisingly, no reference to the Declaration is made in the preamble to the 1997 Convention on Human Rights and Biomedicine, Chapter V of which deals with scientific research in the field of biology and medicine. This relatively short Chapter comprises only four Articles. There is no specific reference to the Declaration in any of these Articles or in the Explanatory Report’s paragraphs that deal with them. However, the Declaration was no doubt consulted in the drafting of Chapter V, not least in the light of the fact that the provisions of Article 16 (Protection of persons undergoing research) are stated to have been “largely inspired” by the 1990 Recommendation. A Protocol on Biomedical Research is now being drafted and it is premature to say whether it will be influenced by the October 2000 version of the Declaration.<sup>89</sup> Readers are referred to a recent paper by one of us (SSF) which provides an overview of the current configuration of international guidelines.<sup>90</sup> They are likewise referred to a detailed (and highly useful) comparative analysis of international and selected national instruments on the ethics of human subjects research.<sup>91</sup> The October 2000 revision of the Declaration of Helsinki is one of the international documents examined.

Many interesting perspectives on international and national legislation and codes, insofar as they relate to consent issues in particular, are contained in a recent paper by Playle.<sup>92</sup> Finally, reference should be made to guidance for ethical review committees in Europe issued by the Brussels-based European Forum for Good Clinical Practice (EFGCP); the purpose of the document is stated in the Introduction as being to “provide complementary guidance and support to the Declaration of Helsinki” and to international GCP guidelines currently in use in Europe.<sup>93</sup>

## **IX. PERSPECTIVES ON THE FUTURE OF RESEARCH ETHICS**

Singer and Benatar have recently published a challenging call to the global community to strengthen the capacity to promote and implement ethical standards in the conduct of medical research involving human subjects.<sup>94</sup> Their paper (which elicited numerous responses) was written after the 2000 revision of the Declaration of Helsinki; they affirm that, in their view, “revisions of this or any other research ethics code are unlikely to make research more ethical throughout the world” without such capacity-strengthening. They cite a recent investigation conducted by the *Washington Post* into research in developing countries which revealed “a booming, poorly regulated testing system that is dominated by private interests and that far too often betrays its promises to patients and consumers”. In an earlier paper, the same authors had discussed another critical issue in medical research in developing countries, namely the standard of care for research participants in developing countries; they offered an “expanded concept” of the standard of care in research, advocating that visiting researchers need a deeper understanding of the social, economic, and political context of trials in such countries.<sup>95</sup>

It would be premature to prejudge the impact of such reports as those of the National Bioethics Advisory Commission in the United States<sup>85</sup> and the Nuffield Council on Bioethics in the United Kingdom (expected to appear in 2001). Suffice it to say that these reports will no doubt be read and reread with interest by the international community of research ethics practitioners and scholars alike. The debate on these reports is likely to be extensive and impassioned, not least because of the several issues on which global consensus remains a dream, at least at the present time.

There have on occasion been calls for harmonisation of the different codes and guidelines that govern the ethics of research on human subjects. This will be a difficult task, not least in the light of the finding (reported to the 159<sup>th</sup> WMA Council Session in May 2001<sup>83</sup>) that there is now a “distinct possibility that fundamental conflicts could occur between the different internationally recognized research ethics guidelines”.

## **X. THE FUTURE OF THE DECLARATION**

At the Pretoria Conference referred to above, the following recommendations were made by the participants:

1. That the WMA conduct an investigation of the implications and implementation of paragraphs 29 and 30 of the revised Declaration of Helsinki to ensure that no good, ethical research is restricted;
2. That the WMA develop a panel of experts to help represent the views of the WMA at the different levels of global debate;
3. That the WMA continues to participate in the wider debate with other stakeholders in research, as outlined in the Concluding Statement [of the Conference].
4. That the WMA collaborates with CIOMS to help harmonize the DoH with the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, which are currently being revised.

The World Medical Association will undoubtedly be guided in its future action regarding the Declaration by these recommendations, as well as by observations on the new revision in the published literature. It can be safely predicted that further commentaries on what are perceived to be sensitive and controversial issues in the Edinburgh text will be forthcoming in the coming months, not least in the light of the final version of the revised 1993 CIOMS guidelines and any relevant developments in other international fora, including the outcomes of successive meetings of the Global Forum on Bioethics in Research. We may conclude this paper by citing the concluding remarks of Koski and Nightingale, writing in mid-2001 in one of the pre-eminent medical journals, about the ethical challenges posed by human subjects research in developing countries:<sup>96</sup>

“Our greatest challenge is to realize and fully accept that in all research involving human subjects, ethics and science are not separable – a given study must conform to ethical standards or it should not be performed, and it must be scientifically sound or it cannot be ethical. The use of a good research design and adherence to sound ethical principles should result in the conduct of research that is valid, reliable, and ethically acceptable in any country. If we can embrace this seemingly simple concept, the ethical dilemmas will not vanish or suddenly become easier to resolve, but we will at least be less likely to conduct activities in the name of science that are disrespectful or harmful to others.”

The World Medical Association, and in particular its Medical Ethics Committee, Council, General Assembly and Secretariat, will undoubtedly be influenced by this statement in the further refinement of the Declaration, a process directed in the final analysis by the need to safeguard and promote human health in developed and developing countries alike, and in particular to protect patients and others in the medical research enterprise.