Primum Non Nocere:
The Continuing Evolution of Safety Monitoring
In Human Subjects Research

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Abstract:

There has been a significant increase in the amount of research conducted on human subjects during the past half-century. Associated with this increase has been a strong focus on mechanisms to monitor and ensure the safety of the subjects enrolled in this research. Much of this focus is a result of a number of highly publicized research abuses, such as those exposed at the Nuremberg trials in 1946. Currently, there are two types of boards in existence to implement these protective measures: Institutional Review Boards and Data and Safety Monitoring Boards. A historical perspective on the evolution of these boards accompanied with an evaluation of their current state is presented here.
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1. Introduction

Practicing physicians are held to very high ethical standards with regards to how they perform patient care. *Primum non nocere* (first, do no harm) is the governing principle behind the standards to which physicians are held, not only by the public, but by themselves as well. However, given the inherent uncertainty and potential harm involved in clinical research, physician-researchers often find themselves in the challenging situation of guarding the safety of their patients while at the same time trying to advance the science of medicine. Surprisingly, the standards to which we currently hold clinicians (practicing physicians) have not always been equally applied to researchers. In fact, much of the relevant legislation we have today is a reaction to the failure of ethics in clinical research. As a result, current physician-researchers, when conducting research involving human subjects, are bound to even higher ethical standards than clinicians. When conducting a study, the researcher’s principal ethical obligation is to design the study “to minimize risk, to ensure the adequate disclosure of the remaining risks to prospective subjects, and to protect individual subjects enrolled in the study.”

Unfortunately, due to certain inherent biases and confounding events, it is often very difficult to ascertain whether or not a given therapy or intervention truly caused the observed effect. For these reasons, the U.S. Food and Drug Administration (FDA) currently requires “substantial evidence” of efficacy from “adequate and well-controlled clinical trials” prior to the approval of any New Drug Application (NDA). The phrase “adequate and well-controlled trials” is generally interpreted to mean that more than one trial has been conducted with concordant and statistically significant results or that a single trial has achieved the statistical standard of two positive trials (P value < 0.00125).

Since its introduction in the late 1940s, the modern randomized controlled trial (RCT) has become widely recognized as the “gold standard” of clinical research. The RCT is described as “the best method available to confirm the value or to test the efficacy of a treatment, to prevent the propagation of worthless treatments, or to document harm caused by a conventionally and widely used therapy.” The use of randomization in treatment assignment in these trials can be controversial and may appear to be counter to the aforementioned ethical standards. The justification of randomization is based on the assumption of clinical equipoise — a “state of genuine uncertainty” on the part of the medical community “regarding the comparative therapeutic merits of each arm in a

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2 21 CFR 314.126
3 The P value represents a statistical measurement of the likelihood that the observed result could have occurred by chance. For instance, a P value of 0.05 indicates that there is only a 5% likelihood that the observed result could have occurred by chance. A P value of 0.05 is generally accepted to be the upper limit of statistical significance.
5 Bobbio M. “To stop or not to stop a clinical trial: that is the problem.” Ital Heart J 2000;1(12):821-823.
However, should equipoise cease to exist, the medical community is ethically obliged to provide the superior therapy. This ethical mandate provides the basis for the early termination of clinical trials, which will be discussed later in great detail.

The rapid growth of clinical research in the past half-century has resulted in an increasing awareness of the ethical issues associated with such research. This heightened awareness has led to close public scrutiny and dialogue among patients, investigators, institutions, and funding agencies. Out of this dialogue have arisen the ethical imperative and the necessary mechanisms to ensure that all human experiments have some form of a “conscience” to guarantee the safety and ethical treatment of the subjects.

Currently, many federal regulations exist regarding the protection of human subjects in research. The enforcement of these regulations is conducted on an institution-specific basis by the appointment of an Institutional Review Board (IRB), which is responsible for the prospective review of research conducted at that institution and for ongoing monitoring to protect the rights and welfare of the involved subjects. However, the ability of an individual IRB to monitor any one of the many large, multi-center trials is extremely difficult and burdensome. As a result, this task is often shared with a trial-specific Data and Safety Monitoring Board (DSMB), which is charged with reviewing the interim trial data and assuring that patient safety and the scientific validity of that study are preserved.

Today, these two types of boards exist as the primary protectors of patient safety in human clinical research. They have not always existed — they evolved out of a growing awareness of the dangers inherent in clinical research and the rights of the human subjects participating in the research. This paper will address the extremely interesting and continuing evolution of the IRB and the DSMB as well as the current challenges with which they are faced today.

2. A Brief History of Controlled Clinical Trials

The first truly modern randomized controlled trial occurred in 1948 with the British Medical Research Council’s study of streptomycin in the treatment of tuberculosis. This trial established the necessary principles for the conduct of large-scale patient randomization; in addition, it formulated “guidelines for the administration of an experimental therapy and the objective evaluation of outcomes.” Prior to this study,

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7 See Freedman, supra note 6.
9 Cairns JA, Hallstrom A, Held P. “Should all trials have a Data Safety and Monitoring Committee?” Am Heart J 2001;141:156-163.
10 See 45 CFR 46
controlled clinical trials were the exception, with most published medical data being limited to observations and statements of opinion. However, there are a few notable exceptions worth mentioning including Lind’s study of scurvy in British sailors (1753) the results of which were largely ignored by the British Admiralty for over 40 years; Louis’ study of bloodletting in pneumonia (1798); and Waterhouse’s study of the smallpox vaccine in orphan teenage boys (1800).

The practice of randomization of research subjects did not originate with the aforementioned British Medical Research Council study, but its origins are not much older. The first published randomization in a controlled trial was actually performed not on patients but on potatoes by Fisher and Mackenzie in 1923 as part of an agricultural study on crop protection. Amberson has been credited with the first use of randomization in a study of human patients in 1931. In a small study of tuberculosis therapy in 24 patients, he used a coin toss to make treatment assignments.

The British Medical Research Council study heralded the beginning of the modern era of clinical research. In the decade that followed this landmark study, the number of publications describing the use of RCTs grew rapidly. In addition, an analysis performed by Max in 2002 of published review articles regarding trial methods during the 1950s noted that the methods in practice during the 1950s were remarkably similar to current practices in trial administration. One of the main distinctions between the 1950s and the current era, is that it was not until the mid-1960s that any significant discussion was had regarding the prospective and continuing review of research by individuals not intimately involved with the conduct of the trial in order to ensure patient safety and study validity.

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16 See Waterhouse B. A prospect of exterminating the smallpox: being the history of variolae vaccinae, or kinepox commonly called the cow-pox; as it has appeared in England; with an account of a series of inoculations performed for the kinepox, in Massachusetts ... (Cambridge, MA). Printed for the author, all at the Cambridge Press, by William Hilliard, and sold by him and the other booksellers in Boston. 1800.
19 See Califf, supra note 12.
21 See Califf, supra note 12.
22 See Califf, supra note 12.
23 See Max, supra note 13.
3. Ethics in Medical Research and the Origins of the Institutional Review Board

Concerns about medical ethics have a long history, but until the mid-1900s the discussion was focused primarily on clinical medicine, not research.\(^{24}\) In 1946, the ethics of human experimentation for medical research was brought to public attention as a result of the Nuremberg trial during which 23 Nazi physicians were tried for crimes committed against prisoners of war and prisoners in concentration camps. These crimes included “exposure of humans to extremes of temperature, performance of mutilating surgery, and deliberate infection with a variety of lethal pathogens.”\(^{25}\) The Nuremberg Code\(^{26}\) was established as a result of this trial to codify fundamental ethical standards for the conduct of research involving human subjects.\(^{27}\) The Code defines 10 specific criteria each of which must be satisfied to justify research involving human subjects.\(^{28}\) The first two conditions are of particular importance as they established the requirement for the “voluntary consent of the human subject” and a scientifically valid research design expected to “yield fruitful results for the good of society” provided that this information is “unprocurable by other methods or means of study.”\(^{29}\)

The importance and broad acceptance of the Nuremberg Code was initially indicated when it was adopted by the United Nations into international law on December 11, 1946.\(^{30}\) Further, in 1948, the principles espoused by the Nuremberg Code were reflected in the United Nations Declaration of Human Rights and were accepted in principle by each of the 51 original signatory nations of the Charter of the United Nations.\(^{31}\) However, despite the existence and acceptance of the Nuremberg Code, its implications were not widely appreciated in United States.\(^{32}\) In fact, even those physician-researchers who were familiar with the Code generally believed that it only applied to research conducted in Germany and that it had little applicability to research conducted in the United States.\(^{33,34}\)

Interestingly, a significant amount of clinical research was done in the United States during the 1950s and throughout the mid-1970s that was clearly in violation of the first condition of the Code – the voluntary consent of subjects who are able to exercise free power of choice. During this time period, many chemotherapeutic agents intended for treatment of cancer and other diseases were initially tested in healthy prisoners; in fact, some pharmaceutical companies even maintained active research facilities at or near


\(^{25}\) Wichman, supra note 24.

\(^{26}\) See Nuremberg Code, Appendix A.

\(^{27}\) See Wichman, supra note 24.

\(^{28}\) See Wichman, supra note 24.

\(^{29}\) Nuremberg Code, Appendix A.

\(^{30}\) See United Nations General Assembly resolution 95(I) of 11 December 1946.

\(^{31}\) See Wichman, supra note 24.

\(^{32}\) See Wichman, supra note 24.

\(^{33}\) See Wichman, supra note 24.

prisons. Another shocking violation came to light in the early 1970s when it was revealed that since 1932, approximately 400 black men in Tuskegee, Alabama had been involved, without their knowledge or consent, in a lengthy study on the natural history of syphilis (the Tuskegee Untreated Syphilis Study). These unfortunate men were systematically denied penicillin even after its introduction as the standard treatment of the disease. It has been suggested that one of the reasons the Code was not always upheld (as in these examples) was that most countries that accepted the principles of the code, including the United States, had no regulatory or procedural mechanism for implementing those provisions. However, the subsequent introduction of such provisions is a direct result of the Tuskegee study and others like it.

In 1953, the NIH opened the Clinical Center (CC), its first major research hospital, which was located in Bethesda, Maryland. The first U.S. federal policy on the protection of human subjects participating in research was developed out of this institution. This policy required that for all studies conducted at CC, prospective review of the research and informed consent of the subjects were to be obtained prior to initiation of the study. These requirements marked the beginnings of what would eventually become Institutional Review Boards. However, there existed an important caveat regarding these requirements, which was that they were only applicable to research involving healthy volunteers; research involving patients was not subject to this policy. This exclusion, while shocking today, was consistent with the predominant thinking of physician-researchers at the time. Physician-researchers argued that establishing explicit rules for the conduct of human research would impede research and "undermine patient trust in the physician."

Later, in the 1960s, with the expansion of federal funding of clinical research, there was also an increase in the number of individuals participating as research subjects. This increase, in conjunction with a number of highly publicized clinical research abuses, reignited interest in the rights of research subjects. Examples of research abuses were common, including a number of newspaper reports in New York identifying researchers that were injecting, without consent, live cancer cells into elderly indigent people to better understand the human immune system. Apparently, no harm befell these subjects, but the investigators were cited for fraud, deceit, and unprofessional conduct. In response to these and many other allegations, the World Health Organization (WHO) recognized the need for broader guidelines than those provided by the Nuremberg

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35 See Wichman, supra note 24.
36 See Wichman, supra note 24.
38 See Wichman, supra note 24.
39 See Wichman, supra note 24.
40 See Wichman, supra note 24.
41 See Wichman, supra note 24.
42 See Wichman, supra note 24.
43 See Wichman, supra note 24.
44 See Wichman, supra note 24.
45 See Wichman, supra note 24.
As a result, The Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects was adopted by the World Medical Society in 1964. These guidelines continue to be in wide use throughout the world and were most recently revised in 2004.

Despite these guidelines the medical community was stunned in 1966 by Dr. Henry Beecher, a highly respected physician-researcher from Harvard Medical School, who reported that “unethical and questionably ethical practices” were common in clinical research conducted at many of the premier research institutions of the United States. In his paper “Ethics and Clinical Research,” he detailed 22 representative examples of unethical experiments on humans conducted by unnamed (but renowned) investigators between 1948 and 1965. Some of the more striking examples include: performance of thymectomies on children undergoing heart operations to study growth and development; severe reduction of patients’ blood pressures to study mental confusion; suturing mercury-filled resistance gauges to the left ventricles of adult patients with heart disease to study their cardiac output; purposely feeding Hepatitis A virus to mentally retarded children; and the injection of live cancer cells into senile and demented patients.

Also in 1966, the NIH promoted the first Public Health Service Policy on the Protection of Human Subjects. This policy required prospective review of research conducted or supported by the Department of Health, Education, and Welfare (HEW) (which included NIH). The purpose of this review was to take into account “the rights and welfare of the subjects involved, the appropriateness of the methods used to secure informed consent, and the risks and potential benefits of the research.”

In the early 1970s, as previously mentioned, information regarding the Tuskegee Untreated Syphilis Study was brought to light, and as a result, the U.S. Senate Committee on Labor and Human Resources convened to hold hearings on this study as well as on other alleged healthcare abuses of prisoners and children. The outcomes of these hearings were:

1. Enactment of the National Research Act of 1974 requiring HEW to codify its policy for the protection of human subjects into federal regulations, which it did in 1974;
2. Formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research;
3. Imposition of a moratorium on research conducted or supported by HEW involving live human fetuses until the National Commission

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46 See Wichman, supra note 24.
47 See Declaration of Helsinki, Appendix B.
48 Wichman, supra note 24.
50 See Beecher, supra note 49.
51 See Wichman, supra note 24.
52 Wichman, supra note 24.
53 See Wichman, supra note 24.
could study and make recommendations regarding this type of research.\textsuperscript{54}

As a result of the above hearings, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created in 1974. This commission operated until 1978 and made numerous recommendations for improvement in the existing HEW regulations and issued numerous reports on the ethics of research.\textsuperscript{55} The most notable of these reports was The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.\textsuperscript{56} This report was considered a major advance in public policy by providing "guidance for distinguishing therapeutic medicine from research, [identifying] three fundamental ethical principles for the protection of human subjects, and [illustrating] how the ethical principles should be applied to conduct of human subjects research."\textsuperscript{57} The three fundamental principles identified are respect for persons, beneficence, and justice. The principle of respect for persons acknowledges the dignity and autonomy of subjects and requires that individuals with diminished autonomy be provided special protection.\textsuperscript{58} The principle of beneficence requires the protection of individuals by maximizing anticipated benefits and minimizing possible harms.\textsuperscript{59} Finally, the principle of justice simply requires fair treatment of subjects.\textsuperscript{60}

Following the completion of the above commission operations, HEW, in 1979, began the process of revising its 1974 regulations. However, final approval of 45 CFR 46, Regulations for Protection of Human Subjects, was not given until January 1981 by the Department of Health and Human Services (HHS) (renamed from HEW).\textsuperscript{61,62} In June 1991, the core of these regulations (Subpart A)—referred to as the Common Rule—was adopted by 16 other federal agencies thus extending these regulations beyond research conducted or support by HHS.\textsuperscript{63} The Common Rule formally defines what constitutes research, defines what constitutes a human subject, and provides the requirements and functions for Institutional Review Boards.

\begin{itemize}
\item \textsuperscript{54} Wichman, supra note 24.
\item \textsuperscript{55} See Wichman, supra note 24.
\item \textsuperscript{57} Wichman, supra note 24.
\item \textsuperscript{59} See Gray Booklet, supra note 58.
\item \textsuperscript{60} See Gray Booklet, supra note 58.
\item \textsuperscript{61} See Wichman, supra note 24.
\item \textsuperscript{62} See Regulations for Protection of Human Subjects, 45 CFR 46.
\item \textsuperscript{63} In addition to HHS and FDA, the following departments and agencies adopted the Common Rule: the Departments of Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, and Transportation; The National Aeronautics and Space Administration; the Consumer Product Safety Commission; the Agency for International Development; the Environmental Protection Agency; the National Science Foundation; the Central Intelligence Agency and the Social Security Administration. See Wichman, supra note 24.
\end{itemize}

Most proposed research is required by HHS and FDA regulations to undergo prospective review by an IRB to “review the ethics, the scientific soundness, the relevance of the intervention, and the patient consent process.”64 The purpose of prospective review of research is important to assure the rights and welfare of the human subjects involved in the proposed research. These independent assurances are important as clinical investigators have an inherent conflict of interest when conducting human subjects research.65

In addition to a prospective review of each study to be conducted, the IRB is charged with “continuing review of research … at intervals appropriate to the degree of risk, but not less than once per year.”66 However, the IRB does have the right to allow a third party to observe the consent process and the continuing research in its place.67 However, the IRB maintains responsibility for the local oversight of overall patient safety.68 To ensure patient safety, an IRB may suspend, modify, or terminate approval of research if it is not being conducted in accordance with IRB requirements or if serious harm to subjects has been observed.69,70

The requirements for the establishment and operation of an IRB are set forth in 45 CFR 46 – Protection of Human Subjects. Research is defined as “systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge.”71 A human subject is defined as a “living individual about whom an investigator … conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”72

The membership of an IRB is defined in 45 CFR 46.107 and requires that “each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.” In addition, it further states that “the IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.” It is also charged with ensuring that no IRB consists “entirely of men or entirely of women.” The regulations require that it have at least one member whose primary concerns are in scientific areas, one member whose

64 DeMets DL, Califf RM. “Lessons Learned From Recent Cardiovascular Clinical Trials: Part II.” Circulation 2002;106;880-886.
65 See Wichman, supra note 24.
66 45 CFR 46.109(e)
67 See 45 CFR 46.109(e)
68 See DeMets, supra note 64.
69 See Wichman, supra note 24.
70 See 45 CFR 46.113
71 45 CFR 46.102(d)
72 45 CFR 46.102(f)
primary concerns are in non-scientific areas, and one member who is not otherwise affiliated with the institution.

The criteria under which research can be approved are established in 45 CFR 46.111. These criteria include that:

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(3) Selection of subjects is equitable.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative.

(5) Informed consent will be appropriately documented.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.\textsuperscript{73}

Prospective IRB evaluation entails review of the trial protocol, relevant background information, the informed consent document, proposed plans for informing participants about the trial, and any other procedures associated with the trial. For ongoing trials, the IRB is responsible for considering available information arising from the trial including adverse events and interim findings as well as external data, such as recent literature that may bear on the continued acceptability of the trial at that site.\textsuperscript{74} Unlike a DSMB, an IRB does not generally review unblinded interim data from the trial and so often relies on the

\textsuperscript{73} 45 CFR 46.111

DSMB’s recommendations to the trial sponsor (the organization or institution conducting the trial). 75

All trials conducted under an Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) are subject to federal requirements for prompt reporting of adverse events. 76 Individual investigators are responsible for reporting local adverse events to their IRB; 77 however, in IDE trials, the sponsor is responsible for notifying all involved IRBs of any unanticipated adverse events. 78 In addition, the sponsor is responsible for reporting serious unexpected events to FDA. 79 The IRB does not have a significant role in the communication of adverse events to FDA, but does use the information it obtains to assess the continued viability of the study at that institution.

IRBs conducting continuing review of research may rely on a current statement from the DSMB or sponsor indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. However, the IRB must still receive and review reports of local, on-site adverse events and unanticipated problems. 80

In summary, an IRB has many responsibilities established through HHS regulations which include that “institutions have written procedures which the IRB will follow for (a) conducting its continuing review of research and for reporting its findings and actions to the investigator and the institution, and (b) determining which projects require review more often than annually.” 81 Furthermore, “except when an expedited review procedure is used, each IRB reviews proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in the nonscientific areas.” 82 Finally, “an IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less than once a year.” 83

5. Effectiveness of Institutional Review Boards

The importance of IRBs is clearly evident from their history, but their current operational effectiveness has been recently called into question, most particularly, in a report from the Inspector General’s Office 84 in 1998. This report recognized that the effectiveness of

76 See 21 CFR 312.32(c), 21 CFR 312.51, 21 CFR 812.46(b), 21 CFR 812.150(b)(1). See FDA, supra note 75.
77 See 21 CFR 312.66 (drugs) and 21 CFR 812.150(a)(1) (devices).
78 See 21 CFR 812.150(b)(1). See FDA, supra note 75.
79 See 21 CFR 312.52. See FDA, supra note 75.
80 See HHS, supra note 74.
81 45 CFR 46.103(b)(4).
82 45 CFR 46.108(b).
83 45 CFR 46.109(e). See HHS, supra note 74.
IRBs in their current state is in jeopardy because they face major changes in the current research environment; they review too much, too quickly, and with too little expertise; they conduct minimal continuing review of approved research; they face conflicts that threaten their independence; they provide minimal training for investigators and board members; and neither IRBs nor HHS devote much attention to evaluating IRB effectiveness.\textsuperscript{85}

The first IRBs and their associated regulations were initially established in a time when research was typically conducted by a single investigator receiving government funding on a small cohort of human subjects in a university teaching hospital. However, this environment has changed dramatically since the 1970s as a result of "the expansion of managed care, the increased commercialization of research, the proliferation of multi-center trials, new types of research, the increased number of research proposals, and the rise of patient consumerism."\textsuperscript{86} Each one of these changes presents a significant challenge for an IRB and federal regulations have not been sufficiently updated to meet these new needs.\textsuperscript{87}

The overextension of IRBs is especially apparent in many of the larger research institutions. The Inspector General report cites "expanded workloads, resource constraints, and extensive federal mandates" as contributing to a "rushed atmosphere" where adequate consideration of research is frequently not possible.\textsuperscript{88} In addition, an IRB may face a significant challenge in obtaining the necessary scientific expertise required to reach an informed judgment.\textsuperscript{89}

Given the overextension of IRBs already described, it is no wonder that the continuing review of approved research is often neglected, as there is often little time to go beyond the most basic obligations.\textsuperscript{90} This is particularly relevant in multi-center trials where the IRB is often isolated from the other entities involved in the trial and as a result frequently has minimal information about how the informed consent process works and how well patients rights are being looked after.\textsuperscript{91} In this context, it is not surprising that Dr. John Cairns (a prominent physician-researcher and Dean of the Faculty of Medicine at the University of British Columbia) argues that the practice of an individual IRB monitoring the conduct of its own institution in a multi-center trial without any communication with the other IRBs "makes no sense."\textsuperscript{92} The purpose of the requirement for continuing review is to ensure that as the trial proceeds, local and individual judgments can be made about the continuing equipoise of the trial.\textsuperscript{93} However, given the minimal attention the continuing review process receives from IRBs and that when investigators and IRBs are notified of individual adverse events without an overall baseline for comparison, it

\textsuperscript{85} See Inspector General, supra note 84.
\textsuperscript{86} Inspector General, supra note 84.
\textsuperscript{87} See Inspector General, supra note 84.
\textsuperscript{88} Inspector General, supra note 84.
\textsuperscript{89} See Inspector General, supra note 84.
\textsuperscript{90} See Inspector General, supra note 84.
\textsuperscript{91} See Inspector General, supra note 84.
\textsuperscript{92} Cairns, supra note 9.
\textsuperscript{93} See Fisher, supra note 4.
becomes impossible to put these reports into context and as a result can seriously confuse the issue of trial monitoring.  

The ability to maintain independence on the part of the IRB with respect to the research they monitor is also increasingly difficult. The IRB is responsible to both its institution and to the subjects that it represents. Given that clinical research provides revenue and prestige to the institution, an IRB may find itself in the challenging situation in which it must balance these interests with those of patient safety. In addition, the minimal outside representation on IRBs is frequently insufficient to provide the important counterbalance to institutional interests for which it was intended.  

As clinical trials methods become more complicated and areas of research more advanced, the education and training of the investigators and board members becomes increasingly important. Unfortunately, in the current IRB system, little educational outreach is offered to investigators regarding upholding human subject protections. In addition, little education about the actual research to be conducted is provided for IRB members, which is particularly detrimental to the non-scientific and non-institutional members of the board.  

Finally, little effort has been expended to determine the effectiveness of individual IRBs and the IRB system in general. It is rare that an individual IRB will perform the self-analyses required to determine if they are accomplishing their mission. In fact, most IRBs evaluate their effectiveness based on the number of reported protection lapses or complaints brought to their attention.  

Despite these significant criticisms, the Inspector General’s report presents a number of recommendations aimed at improving the current nature of IRBs such that they will be better equipped to handle their responsibilities to patient safety.  

The first recommendation is that federal IRB requirements should be recast such that they grant IRBs greater flexibility, but also hold them more accountable for results. This recommendation includes the elimination or at least the lessening of some of the procedural requirements directed to IRBs. In addition, it endorses a requirement that IRBs should undergo regular performance-focused evaluations.  

The second recommendation is to strengthen the continuing protections for human subjects participating in research. Implementation of this recommendation would require the use of DSMBs for multi-center trials, which routinely provide feedback on

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94 See Fisher, supra note 4.  
95 See Inspector General, supra note 84.  
96 See Inspector General, supra note 84.  
97 See Inspector General, supra note 84.  
98 See Inspector General, supra note 84.  
99 See Inspector General, supra note 84.  
100 See Inspector General, supra note 84.  
101 See Inspector General, supra note 84.  
102 See Inspector General, supra note 84.
developments in these multi-center trials. In addition, it would require the routine provision of feedback to IRBs about FDA actions against investigators at the institution’s site. It would also require that sponsors and investigators notify their IRBs of any prior reviews of proposed research plans. Lastly, it would call for increased IRB awareness of on-site research practices.

The importance of the use of a DSMB is that it provides a mechanism where true statistical analyses can be performed on reported events to determine whether or not they are “simply part of the background events that typically occur with the disease under investigation.” An additional benefit to the IRB is that FDA routinely reduces the reporting requirements of significant adverse events (SAEs) for trials monitored by DSMBs. Waivers are frequently provided such that SAEs that are also trial end points do not have to be reported in an expedited fashion; however, SAEs no falling into this category must still be reported expeditiously. In a cardiovascular trial, examples of such adverse events might include: acute liver failure, blood dyscrasias, seizures, and allergic bronchospasm. If the trial sponsors fails to obtain these waivers, it places an enormous burden on the local IRB.

The third recommendation is to enact federal requirements to help ensure that investigators and IRB members are adequately educated about and sensitized to human subject protections. This recommendation would require that research institutions have programs for educating its investigators and board members on these protections. In addition, it would require that investigators provide a written attestation of their familiarity with and commitment to such protections.

The fourth recommendation is to help insulate IRBs from conflicts that may compromise their mission of protecting human subjects. This would require increased representation of non-scientific and non-institutional members on IRBs. It would also require mechanisms to reinforce to the institutions the importance of IRBs having sufficient independence. Lastly, it would prohibit equity owners of the institution from participating in the IRB review process.

The fifth recommendation is to ensure recognition of the seriousness of the workload pressures faced by many IRBs and to take actions to moderate these pressures. The

103 See Inspector General, supra note 84.
104 See Inspector General, supra note 84.
105 See Inspector General, supra note 84.
106 See Inspector General, supra note 84.
107 Fisher, supra note 4.
108 See Fisher, supra note 4.
109 See Fisher, supra note 4.
110 See Fisher, supra note 4.
111 See Fisher, supra note 4.
112 See Inspector General, supra note 84.
113 See Inspector General, supra note 84.
114 See Inspector General, supra note 84.
115 See Inspector General, supra note 84.
116 See Inspector General, supra note 84.
main requirement to implement this recommendation is to ensure that IRBs have adequate resources to conduct their work appropriately and in a timely fashion.\textsuperscript{117} Unfortunately, the report does not specify any mechanisms to provide these extra resources.

The final recommendation is to completely reengineer the federal oversight process requiring revamping the FDA on-site inspection process and requiring the registration of all trials.\textsuperscript{118} The registration of clinical trials is a timely topic that is discussed in more detail in the \textit{Publication of Results and Decision Making} section later in this paper (section 8.5).

6. Origins of Data and Safety Monitoring Boards

The previous section established much of the history of the federal and international regulations regarding conduct during clinical research and the origins of the Institutional Review Board. However, while these regulations are important, these requirements are primarily prospective in that they establish what types of research will be allowed. Until the mid-1960s there was little discussion of the establishment of independent advisory groups of experts to help conduct trials as opposed to determining whether or not they should be allowed. These advisory groups came to be known as Data and Safety Monitoring Boards (DSMB).

One of the earliest DSMBs organized was an ad hoc group created to monitor the University Group-Diabetes Project (UGDP)\textsuperscript{119} in the late-1960s.\textsuperscript{120} The purpose of this study was to compare the use of tolbutamide, an oral hypoglycemic agent, with insulin in the evaluation of vascular complications in diabetic patients.\textsuperscript{121} The ad hoc group was organized when trouble began to emerge from ongoing monitoring of the study.\textsuperscript{122} Unfortunately, given the lack of experience with interim data analysis at the time of the trial, outcome data was reviewed on a regular basis in an unblinded fashion.\textsuperscript{123} After some time, patients in the tolbutamide arm were judged by this ad hoc group to have an excess cardiovascular mortality rate, and the trial was subsequently terminated early.\textsuperscript{124} The decision to terminate this trial early resulted in considerable concern among the clinical community and was the subject of many subsequent articles.\textsuperscript{125} As a result of this trial, there has been a long-standing warning on the entire class of sulfonylurea medications (of which tolbutamide is a member) indicating increased risk for...

\textsuperscript{117} See Inspector General, \textit{supra} note 84.

\textsuperscript{118} See Inspector General, \textit{supra} note 84.


\textsuperscript{120} See Cairns, \textit{supra} note 9.

\textsuperscript{121} See Cairns, \textit{supra} note 9.

\textsuperscript{122} See Cairns, \textit{supra} note 9.

\textsuperscript{123} See Cairns, \textit{supra} note 9.

\textsuperscript{124} See Cairns, \textit{supra} note 9.

\textsuperscript{125} See Cairns, \textit{supra} note 9.
cardiovascular mortality. However, this finding has not been confirmed in subsequent studies and the recent UK Prospective Diabetes Study (UKPDS) did not show any evidence of increased mortality in patients treated with sulfonylureas.

Partly as a result of the initial UGDP experience and the fact that the US National Institutes of Health (NIH) was beginning to sponsor large multi-center trials, the then National Heart Institute (now the National Heart, Lung and Blood Institute (NHLBI)) commissioned a task force (the Heart Special Project Committee) under the leadership of Dr. Bernard Greenberg of the University of North Carolina to develop an advisory document concerning the organization and conduct of clinical trials. The resulting report, commonly referred to as the Greenberg Report, was released in 1967 (but was not formally published until 1988). One of the major recommendations from this report was that “every clinical trial should have provision for data and safety monitoring” and that “the mechanism(s) for data and safety monitoring should be presented to and approved by the Institutional Review Board as an integral part of its review of the project proposal.” The report also recommended that an advisory group of experts not directly involved with the trial provide this data and safety monitoring role. As part of this role, the report recommended providing a mechanism for terminating a trial early if it became clear that “the trial could not meet its objectives or new information rendered it superfluous.” The basis for these recommendations comes from the knowledge that interim data monitoring is essential to ensure the safety of the trial subjects and that those individuals responsible for the design and conduct of the trial may not be able to be fully objective in their analysis of the interim data.

The first study to implement the recommendations and operational model of the Greenberg Report was a National Heart Institute trial in the mid-1960s—the Coronary Drug Project (CDP). The CDP was a multi-center, multi-arm placebo-controlled trial designed to evaluate the effectiveness of five lipid-lowering treatments. A Policy

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128 See Collins, supra note 126.
129 See Cairns, supra note 9.
132 Greenberg Report, supra note 131.
134 Ellenberg, supra note 130, p.5
135 See FDA, supra note 75, p.2
137 See Ellenberg, supra note 130, p.6
Advisory Board (PAB) was established to review the conduct of the trial and a special subcommittee was formed within the board to specifically monitor patient safety and efficacy. As a result of this subcommittee’s recommendations, three of the five treatment arms (high- and low-dose estrogen and dextrothyroxine) were terminated early.

Soon after the initiation of CDP, a large number of other trials were implemented with the same basic organizational structure including the use of a DSMB. These trials included the Urokinase Pulmonary Embolism Trial (UPET) in 1968, which was immediately followed by the Urokinase-Streptokinase Pulmonary Embolism Trial (USPET); the Hypertension Detection and Follow-up Program (HDFP) in 1972; the Coronary Artery Surgery Study (CASS) in 1973; the Excorporeal Membrane Oxygenator (ECMO) trial in 1973; the Nocturnal Oxygen Therapy Trial (NOTT) in 1975; the Intermittent Positive Pressure Breathing Trial in 1975; and the Respiratory Distress Syndrome (RDS) Trial in 1975. Thus it can be seen that by the mid-1970s, the establishment of DSMBs was a routine procedure in trials conducted by the NHLBI in many clinical areas, not just heart disease.

Given that the Greenberg Report was not actually published until 1988, there was limited initial use of DSMBs outside of the NIH. However, in 1972, two senior statisticians left the NHLBI to join the newly formed National Eye Institute (NEI). Their experience at NHLBI can be seen in the presence of a DSMB in the Diabetic Retinopathy Study (DRS), one of the first NEI randomized trials.

Later, in the mid-1970s, the Veteran’s Administration (VA) developed guidelines of their own for the planning and conduct of clinical trials on VA patients in their Cooperative Group network. These guidelines, which are regularly revised and updated (most recently in March, 2004), require the use of DSMBs in all Cooperative Group Studies.

The increasing use of DSMBs by federally funded agencies continued to expand in the 1980s when trials sponsored by the National Cancer Institute (NCI) began to incorporate them. The first group to establish a DSMB for a cancer trial was the North Central Cancer Treatment Group (NCCTG), based at the Mayo Clinic. However, the model that NCCTG used for their DSMB was somewhat different than that put forward by the Greenberg Report. Instead of using an independent group of outside experts, their DSMB

138 See Ellenberg, supra note 130, p.6
139 See Ellenberg, supra note 130, p.6
140 See Ellenberg, supra note 130, pp.6-7
141 See Ellenberg, supra note 130, p.7
142 See Ellenberg, supra note 130, p.7
144 See Ellenberg, supra note 130, p.7
145 See Ellenberg, supra note 130, p.8
147 See Ellenberg, supra note 130, p.8
involved study investigators and a statistician from the group’s coordinating center. While not independent, the use of a DSMB was still a major advance in the conduct of cancer trials in that it established a new approach of not sharing interim data amongst all the investigators, which at that time was the standard practice in cancer trials. The traditional requirements for DSMBs are somewhat different in cancer trials as the trials are generally unblinded due to the complex nature of administration of chemotherapy and the distinctive toxicities associated with different agents. Nonetheless, DSMBs have been found to be a valuable component of clinical cancer research.

Much like the introduction of the DSMB to the NEI, the Southwestern Oncology Group (SWOG) introduced DSMBs to their studies after two NCCTG statisticians moved to SWOG. Shortly thereafter, these two organizations participated in an intergroup study of adjuvant chemotherapy for colon cancer, which provided the other participating cancer cooperative groups their first exposure to this operational model. As a result of this study and a 1994 publication on data monitoring polices by the NCI, many other cancer cooperative groups have established DSMBs as part of their studies.

The advent of the AIDS epidemic in the early 1980s led to many new challenges in the conduct of clinical trials including an unprecedented level of involvement from patient representatives and advocacy groups as well as scientific and political pressures to rapidly discover an effective therapy. In addition to the obvious widespread public interest in these trials, the pharmaceutical industry was much more closely involved than had been traditional with other NIH-sponsored clinical trials. In response to this epidemic, the National Institute of Allergy and Allergic Diseases (NIAID) formed two clinical trial networks: the AIDS Clinical Trial Group (ACTG) and the Community Programs for Clinical Research in AIDS (CPCRA). A unique feature of these groups is that they were served by a single DSMB, which worked to develop operational approaches to deal with these many new challenges.

Since the late-1970s, the NIH has issued many policy notices regarding data and safety monitoring. In 1979, the NIH Clinical Trials Committee recommended that “every

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148 See Ellenberg, supra note 130, p.8
149 See Ellenberg, supra note 130, p.8
150 See Ellenberg, supra note 130, p.8
152 See Ellenberg, supra note 130, p.8
153 See Ellenberg, supra note 130, p.8
155 See Ellenberg, supra note 130, p.8
156 See Ellenberg, supra note 130, pp.8-9
157 See Ellenberg, supra note 130, p.9
158 See Ellenberg, supra note 130, p.8
159 See Ellenberg, supra note 130, p.8
clinical trial should have provision for data and safety monitoring."\textsuperscript{160} However, they further acknowledged that "a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial. In many cases, the principal investigator would be expected to perform the monitoring function."\textsuperscript{161} Then in 1994, the Office of Extramural Research established the Committee on Clinical Trial Monitoring to review the oversight of phase III clinical trials. They made a strong recommendation that "all trials, even those that pose little likelihood of harm, should consider an external monitoring body."\textsuperscript{162} In 1998, the NIH issued a new policy stating that "the establishment of the data safety monitoring boards (DSMBs) is required for clinical trials involving interventions that entail potential risk to the participants."\textsuperscript{163} Finally, in 2000, the NIH issued its most recent notice to further provide guidance for phase I and II trials which states that for "earlier trials (phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations."\textsuperscript{164}

While the use of DSMBs was common and often required in government sponsored trials, few trials sponsored by the pharmaceutical/medical device industry incorporated DSMB oversight until relatively recently. Of those few-industry sponsored trials utilizing DSMBs, the majority were studies of cardiovascular disease and had improvement of survival as their primary endpoint, following the model established by the NHLBI.\textsuperscript{165} An additional reason for the lack of DSMBs in industry-sponsored trials is that the majority of clinical trials sponsored by pharmaceutical companies were attempting to determine whether or not a particular agent relieves a symptom of disease, as opposed to evaluating a morbidity or mortality endpoint.\textsuperscript{166} Despite these aforementioned reasons, DSMB use has grown significantly in industry-sponsored trials; FDA has identified three main reasons in particular for this change. The first is the "growing number of industry-sponsored trials with mortality or major morbidity endpoints,"\textsuperscript{167} which is potentially related to the increasing skepticism over the reliability of surrogate endpoints.\textsuperscript{168} The second is the "increasing collaboration between industry and government in sponsoring major clinical trials, resulting in industry trials performed under the policies of government funding agencies, which require the use of DSMBs."\textsuperscript{169} The third is the "heightened awareness within the scientific community of problems in clinical trial


\textsuperscript{161} NIH, \textit{supra} 160.

\textsuperscript{162} NIH, \textit{supra} 160.

\textsuperscript{163} NIH, \textit{supra} 160.


\textsuperscript{165} See Ellenberg, \textit{supra} note 130, p.9

\textsuperscript{166} See Cairns, \textit{supra} note 9.

\textsuperscript{167} FDA, \textit{supra} note 75.

\textsuperscript{168} A surrogate endpoint is an endpoint measured in lieu of another endpoint with the belief that the surrogate endpoint is predictive of outcomes related to endpoint of interest. For instance, cholesterol is frequently used as a surrogate endpoint for cardiovascular mortality in studies evaluating cholesterol reduction. Surrogate endpoints are used because they reduce the period of time that a trial must be conducted for in order to reach a statistically significant result.

\textsuperscript{169} FDA, \textit{supra} note 75.
conduct and analysis that might lead to inaccurate and/or biased results, especially when early termination for efficacy is a possibility, and the demand for approaches to protect against such problems.\textsuperscript{170}

7. Notable Examples of DSMB Actions

There are numerous recent trials whose outcomes have been positively or negatively affected by the recommendations of DSMBs. After reviewing interim data a DSMB can make one of four possible recommendations: continue as designed, termination of study, continuation with major or minor modifications, or temporary suspension of enrollment and/or the investigational therapy until some uncertainty is resolved.\textsuperscript{171} The most important and controversial of these recommendations is early termination. Trials that are terminated are done so for one of three reasons: excess benefit, excess harm, or futility. A few examples of these actions are presented below.

The first example is a trial that was stopped early because of benefit considerations. The Beta-Blocker Heart Attack Trial (BHAT)\textsuperscript{172} was comparing the beta-blocker, propranolol, against placebo in 3837 people who had recently suffered a myocardial infarction. An interim analysis was performed nine months before the scheduled conclusion of the trial, which observed 183 deaths in the placebo group (9.5%) and 135 deaths in the propranolol group (7%).\textsuperscript{173} The DSMB decided to end the trial early because these results were generally consistent with other studies of beta-blockers in similar patients and that the expected number of deaths in the remaining months of the trial would not be enough to change the statistical significance of this result.\textsuperscript{174} In addition, the benefit to patients in the placebo arm and to the entire population of patients being started on beta-blockers outweighed any other remaining concerns.\textsuperscript{175,176}

The second example is that of a trial that was stopped early for harm. The Cardiac Arrhythmia Suppression Trial (CAST)\textsuperscript{177} was designed to investigate whether antiarrhythmic therapy would reduce the incidence of death resulting from arrhythmia in patients with a history of myocardial infarction and frequent premature ventricular contractions (PVCs). At the time it was widely believed that suppression of PVCs would decrease the likelihood of developing a fatal arrhythmia. Patients were initially

\textsuperscript{170} FDA, \textit{supra} note 75.
\textsuperscript{171} See FDA, \textit{supra} note 75.
\textsuperscript{174} See Friedman, \textit{supra} note 173.
\textsuperscript{175} See Friedman, \textit{supra} note 173.
randomized to one of three antiarrhythmic drugs (encainide, flecainide, and morizine).\textsuperscript{178} Once suppression of PVCs on the assigned drug was observed by electrocardiographic monitoring, the patient was then randomized to either the initially assigned drug or placebo.\textsuperscript{179} Early in the study, with roughly 1100 patients (out of a planned 4400) randomized, it was noted that there was a large difference between the two groups with 19 arrhythmic deaths in one group vs. 5 in the other; in addition, total mortality was 31 vs. 15 respectively.\textsuperscript{180} The DSMB opted to remain blinded, as these were small numbers and it was early in the trial, in addition, the DSMB felt that "overwhelming evidence was necessary to offset strongly held prior assertions concerning the clinical value of antiarrhythmics."\textsuperscript{181} Six months later when this trend continued, they opted to unblind themselves. It was noted that there were 35 arrhythmic deaths in the treatment group and 13 in placebo group; total mortality was 60 vs. 33 respectively.\textsuperscript{182} Further analysis revealed that all of the harm was confined to two of the three antiarrhythmic drugs (encainide and flecainide).\textsuperscript{183} Based on this information, the encainide and flecainide arms were discontinued while the third arm (morizine) continued against placebo.\textsuperscript{184} However, as the trial progressed there continued to be a trend towards harm in the treatment group and the DSMB recommended stopping CAST entirely based on the strong overall trend towards harm and the small likelihood that this trend would reverse itself were the trial continued.\textsuperscript{185} The outcome of this trial emphasizes the importance of having adequate statistical power to detect important beneficial and harmful effects, because if this trial had been underpowered (not enough subjects enrolled to achieve a statistically significant result) it might have led to claims of "no harm" when in fact harm was being done.\textsuperscript{186} Very early termination of CAST because of increased risk created a lengthy debate due to its contradiction of widely held beliefs about antiarrhythmics. This was a particularly important trial because its results challenged the predominant thinking of the medical community, and as a result, today, there has been a significant decline in the use of pharmacologic antiarrhythmic therapy in favor of medical devices.

A third example is that of the aspirin component of the Physician’s Health Study, which was terminated early because of futility.\textsuperscript{187} This study was a two-by-two factorial design study of aspirin and beta-carotene in more than 22,000 healthy U.S. male physicians.\textsuperscript{188}

\textsuperscript{178} See Friedman, supra note 173.
\textsuperscript{179} See Friedman, supra note 173.
\textsuperscript{180} See Friedman, supra note 173.
\textsuperscript{181} Armstrong, supra note 8.
\textsuperscript{182} See Friedman, supra note 173.
\textsuperscript{183} See Friedman, supra note 173.
\textsuperscript{184} See Friedman, supra note 173.
\textsuperscript{185} See Friedman, supra note 173.
\textsuperscript{188} See Friedman, supra note 173.
The beta-carotene component was designed to evaluate the effect of beta-carotene supplementation on cancer incidence.\textsuperscript{189} The aspirin component was designed to evaluate whether aspirin reduced cardiovascular mortality.\textsuperscript{190} After several years of study, there was a favorable mortality trend in the aspirin group compared to placebo, but the overall and cardiovascular death rates observed were considerably lower then initially predicted.\textsuperscript{191} Over the next couple of years, a highly statistically significant decrease in the number of myocardial infarctions in the aspirin group was noted.\textsuperscript{192} Despite this decrease in events, the overall cardiovascular mortality rate remained quite low with no significant difference between the study groups.\textsuperscript{193} However, a very small adverse trend for hemorrhage stroke was noted to be developing in the aspirin group.\textsuperscript{194} Based on the lower than expected cardiovascular mortality rate, the aspirin component of the trial was stopped because the DSMB felt that there was an extremely low probability that a significant difference could be detected in cardiovascular mortality without extending the trial for many additional years.\textsuperscript{195} Fortunately, a clear answer regarding aspirin’s protective effect on myocardial infarction had been obtained despite early termination.

In addition to trial termination as discussed above, a DSMB may also make recommendations for trial modification. A demonstrative example can be seen in the Diabetic Retinopathy Study (DRS).\textsuperscript{196} This study was established to evaluate a new photocoagulation treatment in diabetic patients with proliferative retinopathy.\textsuperscript{197} One eye of each study participant was randomly assigned to the new therapy while the other eye received standard medical therapy. However, early on in the study, the DSMB noticed an unexpected large benefit associated with photocoagulation therapy.\textsuperscript{198} Instead of recommending early termination, the DSMB was conservative and recommended that the study continue but that each “control eye” would be followed and once that eye reached a certain level of retinopathy it would cross-over to receive photocoagulation.\textsuperscript{199} This change in protocol allowed for continued long-term evaluation of safety and duration of benefit without violating the ethical mandate of the DSMB.\textsuperscript{200}

8. Current Nature of Data and Safety Monitoring Boards

It is evident that the nature of Data and Safety Monitoring Boards has changed significantly over time, in fact so has the name. This board may be frequently referred to by a number of other names, such as Data Monitoring Committee (DMC), Data Monitoring Board (DMB), Safety and Efficacy Monitoring Committee (SEMC), or

\footnotesize{\textsuperscript{189} See Friedman, supra note 173.  
\textsuperscript{190} See Friedman, supra note 173.  
\textsuperscript{191} See Friedman, supra note 173.  
\textsuperscript{192} See Friedman, supra note 173.  
\textsuperscript{193} See Friedman, supra note 173.  
\textsuperscript{194} See Friedman, supra note 173.  
\textsuperscript{195} See Friedman, supra note 173.  
\textsuperscript{196} See Diabetic Retinopathy Study Research Group, supra note 143.  
\textsuperscript{197} See Ellenberg, supra note 130, pp.7-8  
\textsuperscript{198} See Ellenberg, supra note 130, pp.7-8  
\textsuperscript{199} See Ellenberg, supra note 130, pp.7-8  
\textsuperscript{200} See Ellenberg, supra note 130, pp.7-8}
Treatment Effects Monitoring Committee (TEMC). In its guidance, FDA uses the name DMC, but for consistency with the majority of the available literature, the name DSMB will continue to be used throughout this section.

According to FDA, a DSMB is currently defined as a “group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial” whose purpose is to advise “the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.”

FDA states that trial sponsors “are required to monitor studies evaluating new drugs, biologics, and devices.” There are many individuals and groups that may play different roles in this monitoring, including the sponsor organization, the clinical investigators, the local IRBs, and the DSMB. Despite this FDA mandate for study monitoring, current FDA regulations impose no specific requirements for the use of a DSMB in a trial except in research studies in emergency settings conducted under 21 CFR 50.24(a)(7)(iv), in which the informed consent requirement may be waived. However, in 2002, FDA issued a draft guidance to “assist sponsors of clinical trials in determining when a [DSMB] is needed for optimal study monitoring, and how such committees should operate.” NIH and VA have also established their own rules and requirements for DSMB use in studies funded by those administrations. In fact, NIH and VA require the use of DSMBs for all large, multi-center clinical trials that entail risk to the participants. However, given that FDA’s guidance clearly draws from the examples of NIH and VA, in addition to the fact that FDA has regulatory authority over the approval of NDAs based on their trial designs and outcomes, it is the FDA guidance that will be focused on here.

8.1 When To Establish

Federal regulations require that all clinical trials conduct safety monitoring, but certainly not all trials require the efforts of a DSMB. Historically, DSMBs have generally only been established for large, randomized multi-center studies to evaluate interventions intended to “prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer.” Today, FDA recommends that DSMBs should be established for controlled trials with “mortality and major morbidity as a primary or secondary endpoint.” However, there are many other situations in which a DSMB would be considered beneficial. FDA recognizes that in trials where the participants are at an elevated risk for major adverse outcomes, a DSMB should be

201 FDA, supra note 75.
202 FDA, supra note 75. See 21 CFR 312.50 and 312.56 for drugs and biologics. See 21 CFR 600.80, 812.40, and 812.46 for devices.
203 See FDA, supra note 75.
204 FDA, supra note 75.
205 See NIH, supra note 164. See Cooperative Studies Program, supra note 146.
206 See 21 CFR 312.32(c).
207 See FDA, supra note 75.
208 FDA, supra note 75.
209 FDA, supra note 75.
considered even if the study only addresses lesser outcomes such as relief of symptoms. Cairns suggests a number of additional indications including when any study is large enough to potentially detect important effects on mortality, irreversible morbidity, and “tangible human outcomes.” A DSMB should also be considered when the treatment risk is unknown, as adverse outcomes may occur unpredictably (e.g. unexpected deaths in studies of prostacyclin analogs for treatment of severe congestive heart failure [Flolan International Randomized Survival Trial (FIRST)]) and in gene therapy studies. Two other situations should warrant consideration: when a therapy has a known risk of severe side effects even if being used for a different indication, and when the results of the study will be used to recommend therapy to large populations of patients at risk for major events.

Based on the above recommendations and NIH/VA requirements, it is well established that a DSMB should monitor phase III trials of therapies for diseases with significant morbidity and mortality rates. However, what is less well established is the use of DSMBs in administrative, behavioral, or other psychosocial interventions. While these are often supposed harmless, the same ethical issues arise and some of these interventions may even potentially increase mortality rates; thus, careful consideration should be applied to determine whether a DSMB would be useful.

As a result of the CAST study discussed previously, the use of surrogate end points (PVCs in that case) has been called into question, since in CAST they did not accurately predict the observed effect on mortality. This has led to questions as to whether DSMBs are needed for trials in hypertension and hyperlipidemia, as blood pressure and cholesterol levels are simply surrogate endpoints for risk of cardiovascular morbidity and mortality. However, trials utilizing surrogate end points are often simply discontinued if safety issues do arise. As a result, some clinical investigators have taken the position that therapeutic practices should not be based on the results of small trials using surrogate end points but instead clinical outcome trials should be mandatory in such cases.

When determining whether or not to establish a DSMB, FDA asserts that there are three important factors that must be addressed: “safety, practicality, and scientific validity.” With regards to safety, FDA recommends that the sponsor consider the following questions.

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210 Cairns, supra note 9.
213 See Cairns, supra note 9.
214 See Cairns, supra note 9.
215 See Armstrong, supra note 8.
216 See Cairns, supra note 9.
217 See Cairns, supra note 9.
218 See Cairns, supra note 9.
219 FDA, supra note 75.
Is the study endpoint one for which a favorable or unfavorable early result might ethically require termination of the study before its planned completion? Is there a reason for a particular safety concern? Is the treatment to be tested novel or is there specific prior information that raises concerns for serious toxicity?\textsuperscript{220}

In addition, patient safety concerns are usually heightened in studies performed in potentially fragile populations such as children, prisoners, pregnant women, handicapped or mentally disabled persons, and economically or emotionally disadvantaged persons.\textsuperscript{221} Safety concerns should also be raised in large, lengthy, and/or multi-center trials as they increase the possibility of detecting adverse events because of the overall exposure.\textsuperscript{222}

Another important consideration in the establishment of a DSMB is whether or not such an effort is practical. For instance, a DSMB would normally be considered for a trial with morbidity or mortality outcomes, but if the duration of that trial were short, the sponsor would have to establish specific mechanisms in advance to ensure that the DSMB could be informed and convened quickly as necessary in the event of an unexpected result.\textsuperscript{223} If these practicality issues are not addressed, the likelihood of the DSMB having an adequate opportunity to contribute is greatly diminished.\textsuperscript{224}

Patient safety is not the only benefit provided by a DSMB. A DSMB can also help to ensure the scientific validity of a study, as trials of any appreciable duration are likely to be affected by changes in “understanding of the disease, the affected population, and the standard treatment used outside of the trial.”\textsuperscript{225} These external changes may encourage modification of some aspects of the trial during its progression, such as inclusion criteria, trial endpoints, or size of the trial.\textsuperscript{226} However, if the sponsors and/or investigators are also reviewing the unblinded interim data, this knowledge may potentially influence their decision to make these changes to the study.\textsuperscript{227} This bias will inevitably have a significant negative impact on the validity and credibility of the study results.\textsuperscript{228} Yet, when a DSMB is present and is the only group involved in reviewing unblinded interim data, the sponsors and/or investigators are free to make changes to the trial motivated only by the external data. A DSMB may then provide a “voice of objectivity” when decisions about such a trial must be made.\textsuperscript{229}

Even in an unblinded trial, a DSMB may perform valuable functions because blinding or not blinding has no effect on the overall need for monitoring safety and benefit. Trials of

\textsuperscript{220} FDA, supra note 75.
\textsuperscript{221} See FDA, supra note 75.
\textsuperscript{222} See FDA, supra note 75.
\textsuperscript{223} See FDA, supra note 75.
\textsuperscript{224} See FDA, supra note 75.
\textsuperscript{225} See FDA, supra note 75.
\textsuperscript{226} FDA, supra note 75.
\textsuperscript{227} See FDA, supra note 75.
\textsuperscript{228} See FDA, supra note 75.
\textsuperscript{229} Cairns, supra note 9.
cancer treatments are almost never blinded; yet it has been documented that cancer trials conducted with DSMBs, in contrast to those in which interim results are readily available to all investigators, are more likely to be completed and to provide a consistent message.230

8.2 Organization and Membership

FDA recognizes that there is no single DSMB model that is optimal for all settings and that there is not often a consensus about the optimal model in any given setting.231 The ability of the DMSB to provide the additional assurance of patient safety and trial integrity depends on appropriate selection of DSMB members.

The trial sponsor and/or trial steering committee generally appoint the DSMB.232 Factors that should be considered in the selection process include: relevant expertise, experience in clinical trials, experience on other DSMBs, and a lack of serious conflict of interests.233 There is considerable literature on the issue of conflict of interest with regards to serving on a DSMB. DeMets suggests that “remuneration of DSMB members should not be excessive, but should be provided at usual consultant rates.”234 In addition, DSMB members should have no financial investments (e.g. stock holdings) in, ongoing consultancies with, or other advisory positions with the sponsor.235 Furthermore, they should not have any financial interests outside of the sponsor that could be “substantially affected by the outcome of the trial.”236 Interestingly, however, the US Security and Exchange Commission does not actually prohibit DSMB members from trading on information gained as a result of having access to blinded interim data.237 In addition to all of these types of conflicts of interest, it is also important to be aware of potential “intellectual” conflicts of interest of individuals known to have strong views on the relative merits of the interventions under study.238 For this reason, it is also recommended that DSMB members should not have relationships with individuals in trial leadership positions that could be considered to affect their objectivity.239

A DSMB may have as few as three members, but may often need to be larger due to the nature of the trial.240 Cairns suggests that having an odd number of individuals on the committee is desirable as it ensures that decisions can always be made by a majority if a vote is taken.241 For complex or lengthy trials, it may be appropriate to introduce

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230 See Green, supra note 151.
231 See FDA, supra note 75.
232 See FDA, supra note 75.
233 See FDA, supra note 75.
234 DeMets, supra note 184.
235 See DeMets, supra note 184. See Cairns, supra note 9.
236 FDA, supra note 75.
238 FDA, supra note 75.
239 See FDA, supra note 75.
240 See FDA, supra note 75.
241 See Cairns, supra note 9.
redundancy in the appointment of members to prevent complications that might arise as a result of DSMB attrition or frequent meetings.\textsuperscript{242} However, when possible, it is sensible to keep the DSMB small in size (for logistical reasons) while still being able to represent all of the necessary skills and expertise.\textsuperscript{243}

A typical DSMB is composed of relevant clinical experts and at least one biostatistician knowledgeable about statistical methods for clinical trials and analysis of interim data.\textsuperscript{244} Some DSMBs have also benefited from the inclusion of a medical ethicist on the board. The primary benefit of the medical ethicist will be that individual’s ability to assist in framing the issues that the DSMB should debate.\textsuperscript{245} There is precedent for the inclusion of one or more individuals who are non-scientists to help represent the perspectives of the population under study.\textsuperscript{246} In addition, in trials with substantial public visibility, the addition of a patient advocate can be useful.\textsuperscript{247} For international trials, it is recommended that, to the extent practical, there should be some representation from the participating countries or regions.\textsuperscript{248} When selecting individuals for these positions, prior experience on a DSMB is considered helpful, but not essential.\textsuperscript{249} However, it is important that at least some of the members, in particular the chair, have prior DSMB service.\textsuperscript{250} Also, if there is to be only one statistician involved, it is desirable for that individual to also have had prior DSMB experience.\textsuperscript{251} In addition to filling these important roles, Cairns argues that the selected individuals should have demonstrable experience that prove that the member has both common sense, as well as “nerve,” so that that member will be able to make the difficult decisions usually required of a DSMB.\textsuperscript{252}

Understandably, many companies, which until recently did not make significant use of DSMBs, were reluctant to give up access to accumulating data as the trial progressed. A DSMB that is independent of the sponsor does have many advantages and is considered desirable for many reasons. These reasons include that “principal responsibilities are first to ensure protection of study participants and second to protect the scientific validity of the trial. Independence helps ensure that sponsor interests do not unduly influence the DSMB. It also promotes objectivity that is beneficial in terms of credibility.”\textsuperscript{253} In addition, it prevents sponsors, investigators, media and other parties from having access to interim data, which could easily disturb the assumption of clinical equipoise.\textsuperscript{254} Independence also “preserves the ability of the sponsor to make modifications to the trial in response to external information without introducing bias or skepticism about its

\begin{itemize}
\item \textsuperscript{242} See FDA, supra note 75.
\item \textsuperscript{243} See FDA, supra note 75.
\item \textsuperscript{244} See FDA, supra note 75.
\item \textsuperscript{245} See Cairns, supra note 9.
\item \textsuperscript{246} See FDA, supra note 75.
\item \textsuperscript{247} See Cairns, supra note 9.
\item \textsuperscript{248} See FDA, supra note 75.
\item \textsuperscript{249} See FDA, supra note 75.
\item \textsuperscript{250} See FDA, supra note 75.
\item \textsuperscript{251} See FDA, supra note 75.
\item \textsuperscript{252} See DFA, supra note 75.
\end{itemize}
motives based on the large financial stake it has in the outcome.”\textsuperscript{255} Finally, independence “protects [the] sponsor (and trial) from pressure toward premature disclosure of results due to SEC requirements, fiduciary responsibility, or other business considerations.”\textsuperscript{256} There has been at least one example of a case in which a trial sponsor was protected in the courts from stockholder claims of withholding impending negative results based on the fact that the sponsor was blinded to the interim data because of the use of a DSMB in the trial.\textsuperscript{257}

There are many additional reasons supporting the importance of DSMB independence. One reason is that if the sponsor has access to unblinded data, the risk of further unblinding significantly increases.\textsuperscript{258} FDA highlights this risk in recognizing that individuals with knowledge of interim data “may reveal, or be perceived to reveal, information even inadvertently, e.g. by facial expression or body language.”\textsuperscript{259} Furthermore, it may be impossible for outside evaluators to assess the impact of knowledge of interim data, as it is extremely difficult to ensure that that knowledge will not influence decisions regarding the trial.\textsuperscript{260} These concerns can also be seen in the context of US Security and Exchange Laws; as most US corporations have in place specific employee requirements regarding the purchase or sale of stock to prevent even the appearance of insider trading.

There are typically four models of sponsor involvement in the DSMB: a sponsor representative is a voting member, a sponsor representative is a non-voting member, a sponsor representative is only allowed in open meetings in which unblinded data is not discussed, and there is no sponsor representation on the committee.\textsuperscript{261} FDA considers only the latter two cases to be “independent” committees.\textsuperscript{262} Unfortunately, even in these two “independent” cases, it is nearly impossible for a DSMB to be entirely independent of the sponsor since DSMB members are typically appointed by and paid by the sponsor.\textsuperscript{263}

\textsuperscript{255} FDA, supra note 75.
\textsuperscript{256} FDA, supra note 75.
\textsuperscript{257} A small biotech company sponsored a multi-center randomized double-blind placebo controlled trial (ALS CNTF) to evaluate a new ciliary neurotrophic factor (CNTF) in the patients with amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease. The sponsor established an independent DSMB to monitor the trial and as a result was totally blinded to the interim data. The DSMB terminated the trial early due to adverse events. The sponsor, within a day of notification of the DSMB’s decision, alerted the financial community. Later, investors with great expectations of this therapy brought legal action against the sponsor, arguing that the sponsor had misled them because it had not alerted them early about the impending negative results. However, since the sponsor was blinded to the interim results, they did not know the results until the day before the results were made public. The use of an independent DSMB provided the sponsor with a strong defense against these claims of illegal activity. See Ellenberg, supra note 130, p.10.
\textsuperscript{258} See FDA, supra note 75.
\textsuperscript{259} FDA, supra note 75.
\textsuperscript{260} See FDA, supra note 75.
\textsuperscript{261} See FDA, supra note 75.
\textsuperscript{262} See FDA, supra note 75.
\textsuperscript{263} See FDA, supra note 75.
8.3 Functions and Responsibilities

The fundamental responsibility of every DSMB is to ensure patient safety and study validity by monitoring the accruing interim data of the study and making recommendations based on its analyses as to the continuation of the study.²⁶⁴ The DSMB is not only obligated to protect those subjects enrolled in the trial, it is also charged with protecting and serving prospective subjects who may be recruited into the trial at a later date as well as protecting and serving the entire population of patients worldwide.²⁶⁵ It is also fundamental that the DSMB have the conviction that the proposed trial “to be performed is valid and will yield results of societal benefit commensurate with the risk undertaken by its subjects.”²⁶⁶

In addition to the four primary recommendations regarding continuation previously described, a DSMB may recommend increasing or decreasing surveillance for adverse events or outcomes if there is concern that a particular type of event may not be adequately detected.²⁶⁷ The DSMB may also make other recommendations short of termination that might reduce the risk of adverse events. Possible recommendations could include changing the eligibility criteria if risks are concentrated in one particular subgroup, altering the dosage or schedule of the therapeutic, notifying current and future patients of new risks, and requiring reconsent of current participants.²⁶⁸

Despite all of the possible recommendations available to a DSMB, Armstrong believes that “perhaps the most critical decision the [DSMB] may face is whether or not to recommend that the trial cease because of excess harm or benefit in a treatment group before its planned conclusion.”²⁶⁹ The decision to cease a trial early must be evaluated carefully, because if a trial is inappropriately stopped early, future patients could be exposed to unnecessary risk if another trial were initiated to investigate the same issue.²⁷⁰

When expressing its recommendations, the DSMB should deliver them very clearly to the sponsor in both written and oral form with the opportunity for discussion.²⁷¹ Furthermore, these recommendations and the rationale behind them should be documented in a format that can be easily accessed and reviewed by interested parties including but not limited to the sponsor, IRBs, and involved regulatory agencies.²⁷²

While the majority of recommended protocol changes will have minimal impact on the ability of a trial to obtain regulatory approval, the DSMB should be aware that certain types of changes could have a substantial impact on the validity of the trial and its

²⁶⁴ See FDA, supra note 75. See Armstrong, supra note 8.
²⁶⁵ See Slutsky, supra note 1.
²⁶⁶ Cairns, supra note 9.
²⁶⁷ See Cairns, supra note 9.
²⁶⁸ See FDA, supra note 75.
²⁶⁹ Armstrong, supra note 8.
²⁷⁰ See Armstrong, supra note 8.
²⁷¹ See FDA, supra note 75.
²⁷² See FDA, supra note 75.
subsequent ability to support the desired regulatory decision.\textsuperscript{273} Examples of such changes include “changes in the endpoints, changes in allowed concomitant medications, or in the dose/schedule of the study medication.”\textsuperscript{274} Trial sponsors should address changes of these types with FDA before implementing them.\textsuperscript{275}

As part of the ongoing monitoring process performed by a DSMB, it is responsible for reviewing adverse event data. The trial sponsor normally provides adverse event data to the DSMB in summary form.\textsuperscript{276} However, as discussed earlier with regards to IRBs, the ultimate responsibility lies with the sponsor to review such events promptly and to report serious, unexpected adverse events to FDA.\textsuperscript{277} The benefit of DSMB involvement in this process comes from its ability to help distinguish whether or not the adverse event resulted from the disease being treated or the intervention itself (e.g. myocardial infection in a diabetic patient).

In addition to ongoing safety monitoring, a DSMB is also involved in reviewing study conduct overall and by individual study site. This involves reviewing rates of recruitment, patient ineligibility, noncompliance, protocol violations and dropouts.\textsuperscript{278} It is also involved in assuring completeness and timeliness of data, the degree of similarity between site evaluation of events and centralized review, the balance between study arms on important prognostic variables, and accrual within important subsets.\textsuperscript{279}

Finally, while the DSMB is charged with many great responsibilities, in the end it is still an advisory board.\textsuperscript{280} The sponsor must approve DSMB recommendations, particularly on discontinuation of a trial.\textsuperscript{281} In some situations, FDA may act as a useful second opinion to the sponsor with regards to the implementation of a DSMB recommendation that might affect subsequent regulatory decision-making.\textsuperscript{282}

### 8.4 Statistical Methods

The critical challenge in the analysis of interim data is the determination of when the data cross some statistical boundary and become conclusive enough to justify the early termination of the trial.\textsuperscript{283} When interim data are analyzed multiple times during a trial (a regular occurrence in trials monitored by DSMBs), the use of the standard criteria for statistical significance (P value < 0.05) is an insufficient criterion for stopping a trial early as it can lead to false conclusions due to the effects of multiple tests of

\textsuperscript{273} See FDA, supra note 75.
\textsuperscript{274} FDA, supra note 75.
\textsuperscript{275} See FDA, supra note 75.
\textsuperscript{276} See FDA, supra note 75.
\textsuperscript{277} See FDA, supra note 75. See 21 CFR 312.32 (drugs and biologics) and 21 CFR 812.150(b)(1) (devices).
\textsuperscript{278} See FDA, supra note 75.
\textsuperscript{279} See FDA, supra note 75.
\textsuperscript{280} See FDA, supra note 75.
\textsuperscript{281} See FDA, supra note 75.
\textsuperscript{282} See FDA, supra note 75.
\textsuperscript{283} See Slutsky, supra note 1.
significance.\textsuperscript{284} Essentially, estimates of treatment effect will be unstable at early points in a study and multiple analyses of the interim data will increase the likelihood that a "statistically significant" result may be observed by chance.\textsuperscript{285} As a result, there is real concern that multiple evaluations of the data will lead to an increased Type I error (false positive) rate if no adjustment is made to the analysis to take into account these multiple evaluations.\textsuperscript{286} To prevent this occurrence, FDA recommends specifying in advance, prior to trial initiation, the statistical procedures to be used that will permit multiple interim reviews while still maintaining the Type I error rate at the desired level.\textsuperscript{287} As part of these analyses, statistical boundaries for interim estimates of effect are generated that indicate the magnitude of benefit (or harm) needed to support stopping the trial prior to its planned completion.\textsuperscript{288} An important feature of these boundaries is that their values change over the duration of trial such that as the end of the trial nears, a less stringent P value is required as the results are less likely to change with enrollment of additional subjects, as was the case earlier in the trial.\textsuperscript{289} In addition, the boundaries are frequently asymmetric such that generally greater significance is required in order to terminate for benefit than for harm.\textsuperscript{290} It is important that a trial not be terminated early before a boundary is crossed as the study results will likely be difficult to interpret given the statistical uncertainty coupled with the fact that interim results are likely to exaggerate the magnitude of the effect.\textsuperscript{291}

8.5 Publication of Results and Decision Making

When a trial is terminated early for benefit, the results of that trial are typically available to the public quickly; however, when a trial is terminated early for harm, the public may never learn of these results. In fact, one study investigator noted that "there is no requirement that results be published or even made available to investigators".\textsuperscript{292} Of particular concern, is that only half of the roughly one million trials conducted over the past half-century are likely to have been reported, and of those, a significant proportion did not appear in MEDLINE.\textsuperscript{293} In addition, of those trials that are published, it is relatively rare that the presence or absence of a DSMB is mentioned in the publication.\textsuperscript{294} An unfortunate consequence of this paucity of reporting is that there is a persistent bias in the literature in favor of positive results (commonly called publication bias) and also in favor of the newer or usually more expensive treatments.\textsuperscript{295} This bias is worrisome in that

\textsuperscript{284} See Slutsky, supra note 1.
\textsuperscript{285} See FDA, supra note 75.
\textsuperscript{286} See FDA, supra note 75.
\textsuperscript{287} See FDA, supra note 75.
\textsuperscript{288} See FDA, supra note 75.
\textsuperscript{289} See FDA, supra note 75.
\textsuperscript{290} See Slutsy, supra note 1.
\textsuperscript{291} See FDA, supra note 75. See Slutsky, supra note 1.
\textsuperscript{293} MEDLINE is the world's most comprehensive source of life sciences and biomedical bibliographic information, with nearly eleven million records. It is compiled by the US National Library of Medicine and available online at: http://medline.cos.com. (April 2005). See Rennie, supra note 292.
\textsuperscript{294} See Kiri, supra note 133.
\textsuperscript{295} See Rennie, supra note 292.
harmful effects observed in unpublished trials will likely disappear “without a trace,” since FDA has no mandate to report them to the public. As a result, bad news is almost always disseminated later than the good news or potentially not at all. In fact, one sponsor recently pursued legal action against study investigators to prevent the publication of bioequivalence study results that could hurt sales of its brand-name product (levothyroxine). Similarly, Merck recently forced one of its scientists to remove her name as an author on a study that contained unfavorable results regarding its drug Vioxx.

Despite these issues of publication bias, it has never been the responsibility of a DSMB to publish the results of the trial. However, the importance of careful recording of DSMB deliberations and conclusions cannot be overemphasized, particularly because they may be heavily scrutinized on completion of the trial by numerous interested parties including regulatory agencies. For these reasons, the process by which the DSMB arrives at its decisions should be transparent to an external observer. Implementation of this entails reporting any changes in protocol or procedure made as a result of DSMB decisions to the investigators, IRBs, and FDA. In addition, sponsors are responsible for submitting to FDA “all meeting records, including the non-confidential and confidential interim reports to the DSMB, with the clinical study report.”

As previously mentioned, publication of study results has not generally been held to be an “ethical responsibility” of a DSMB; instead, this responsibility typically falls to the study sponsor, the executive or publication committee, and the principal investigators. However, some have argued that it is an “ethical and scientific imperative” to present and publish harmful negative results as quickly as possible, so that all involved, including future patients, may benefit from these results. In addition, some authors have pushed to make sure that DSMB decisions (even without specific trial data) are made available through journal publication after completion of the trial. A successful example of such behavior can be seen in Wheatley and Clayton’s recent reporting of the rational behind their DSMB decision not to stop a chemotherapy trial funded by the British Medical Research Council in which four courses of chemotherapy for treatment of acute myeloid leukemia (AML) were compared with five courses. Interim analysis (at 50% enrollment) showed lower mortality in the five course group than the four course group

296 Rennie, supra note 292.
297 See Rennie, supra note 292.
298 See Fisher, supra note 4.
300 See Armstrong, supra note 8.
301 See Slutsky, supra note 1.
302 See FDA, supra note 75. See 21 CFR 56.108(a)(3) and (4) and 21 CFR 312.30 for drugs and biologics. See 21 CFR 812.40 for devices.
303 FDA, supra note 75. See 21 CFR 314.50(d)(5)(ii).
304 Fisher, supra note 4.
305 DeMets, supra note 184.
306 See Slutsky, supra note 1.
307 See Slutsky, supra note 1.
(17.1% vs. 27.5%, P value = 0.002). Yet, despite this highly significant result, the DSMB decided not to stop the trial early, because it felt that the treatment effect of the 5th course was “implausibly large.” Fortunately, in the end, their intuition was found to be correct as the mortality rate in the five course group turned out to be slightly, but not significantly, higher (29.2% vs. 25.9%, P value = 0.4).

Unfortunately, an explanation of the decision-making process of the DSMB and its potential implications for research subjects is currently not built into the informed-consent process in most trials. This is problematic because “patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions.” It has also been recognized that individuals who volunteer for research often do so out of altruism and “in return for the altruism and trust that makes clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly.”

Despite these lofty ambitions, selective publication of trial results has long been the norm for a variety of reasons including sponsors not wishing to make unfavorable data about their products available and journals not accepting negative results for publication. In response to this problem, the International Committee of Medical Journal Editors (ICMJE) stated in 2004 that all of their member journals will “require as a consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment.” This is a large step forward in eliminating publication bias and to ensuring that patients’ altruism will be recognized. This requirement for making clinical trials accessible is important as DeAngelis (Editor-in-Chief of JAMA) states:

[R]ather than a single trial, it is usually a body of evidence, consisting of many studies that challenges medical practice. When research sponsors or investigators conceal the presence of selected trials, these studies cannot influence the thinking of patients, clinicians, other researchers, and experts who write practice guidelines or decide on insurance-coverage policy. If all trials are registered in a public repository at their inception, every trial’s existence is part of the public

309 Slutsky, supra note 1. See Wheatley, supra note 308.
310 See Wheatley, supra note 308.
311 See Slutsky, supra note 1.
313 DeAngelis, supra note 312.
314 ICMJE member journals include: Journal of the American Medical Association (JAMA); New England Journal of Medicine; The New Zealand Medical Journal; Norwegian Medical Journal; Canadian Medical Association Journal (CMAJ); The Lancet; MEDLINE; Annals of Internal Medicine; Croatian Medical Journal; Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine); Journal of the Danish Medical Association; and The Medical Journal of Australia.
315 DeAngelis, supra note 312.
record, and the many stakeholders in clinical research can explore the full range of clinical evidence.  

9. When is it Appropriate to Stop a Trial Early?

The nature of clinical equipoise requires that no clinical trial be continued any longer than necessary to evaluate the role of the therapy under investigation; however, frequent interim analysis significantly increases the risk of “false claims of treatment effect, positive or negative.” This results in the complex ethical dilemma to not continue any trial with a significant trend any longer than necessary while still needing to resolve the issue of whether or not this treatment may be beneficial, neutral, or harmful.

For treatments already in common use, the most important decision becomes whether or not it is actually inferior to the other treatment (or lack thereof) under investigation. DSMBs must be careful to consider the effects of casually rejecting the null hypothesis of no treatment effect and to claim harm, as potentially promising drugs might be dismissed too readily. In addition, if a trial is terminated too early, future patients may be put at risk and the significant financial investment in the trial jeopardized. For these reasons, DeMets reminds the community that “early trends with small numbers of patients or events should be interpreted cautiously.” This consideration is also important because adjudication of data can take time, so that all data might not be available at the time of the DSMB’s decision.

Early termination for effectiveness is rarely considered appropriate in studies with less serious outcomes. FDA cites two major reasons for this consideration: “the study may be essentially completed by the time any interim analysis could be undertaken” and “the effectiveness of an intervention to relieve symptoms will generally not be so compelling as to override the need to collect the full amount of safety data.”

Fisher notes that when a DSMB evaluates a trial, it “must carefully weigh and balance a multiplicity of factors: its ethical responsibility to the patients in the trial, which is primary; the prevailing beliefs of the majority of the medical profession; the data needed to promote acceptance of the study findings; related findings pertaining to other drugs, biologics, or devices; and the standards and requirements of regulators.”

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316 DeAngelis, supra note 312.
317 DeMets, supra note 184.
318 See DeMets, supra note 184.
319 See DeMets, supra note 184.
320 The null hypothesis is a statistical hypothesis that there is no difference between for the two or more populations being studied. According to the null hypothesis, any observed difference is due to chance or sampling error. See DeMets, supra note 184.
321 See Cairns, supra note 9.
322 DeMets, supra note 184.
323 See FDA, supra note 75.
324 FDA, supra note 75.
325 Fisher, supra note 4.
It is important that a DSMB be aware that special issues may arise when it recommends actions in a trial subject to regulatory review for registration or product labeling. For example, if a DSMB recommends terminating a study early for treatment benefit but before regulatory criteria have been met, a new study may have to be initiated before the therapy can be approved for marketing. In addition, the early termination may result in a “premature finding or claim” that may make obtaining true informed consent in subsequent trials nearly impossible. As a result, patients may be denied a potentially beneficial therapy because there is not enough adequate evidence for regulatory approval. An important example of such a scenario can be seen in studies of the drug carvedilol. Three similar trials in congestive heart failure (CHF) were performed and these trials were stopped by an independent DSMB that was monitoring all three trials simultaneously as it observed a mortality benefit (P value = 0.001) in the carvedilol groups. Unfortunately, the FDA Cardiovascular and Renal Drugs Advisory Committee denied approval of carvedilol because each of the three studies had defined different primary end points, only one of which has been met when the trial was terminated. It was not until an unusual second meeting took place that FDA recommended approval of carvedilol for marketing.

Despite the regulatory challenges faced by DSMBs, there does not exist a formal mechanism to involve a regulatory agency in the early stages of the trial process. Even if such a mechanism did exist, the early involvement of a regulatory agency might prove to be problematic as it might not be able to provide rapid responses to DSMB questions. In addition, the objectivity of regulatory agencies may be in question as they frequently see related data from similar trials.

One of the most challenging issues is that there are rarely second chances in decision-making related to clinical trials. The inappropriate early termination of a trial may permanently tarnish the reputation of a promising new treatment. A notable example of such an effect can be seen with the sulfonylurea medications previously described. As a result of the hasty decision to stop the UGDP study early; sulfonylurea medications were required to be labeled with a warning for adverse cardiac events, which was later shown to be possibly unnecessary. This example further elucidates the fact that unconvincing premature claims may result in the requirement of an additional trial. Or even worse, no further trials may have been pursued, leaving this important therapy in “limbo.”

326 See Fisher, supra note 4.
327 See Fisher, supra note 4.
328 Fisher, supra note 4.
329 See Fisher, supra note 4.
330 See Fisher, supra note 4.
331 See Fisher, supra note 4.
332 See Fisher, supra note 4.
333 See Fisher, supra note 4.
334 See Fisher, supra note 4.
335 See Fisher, supra note 4.
336 See DeMets, supra note 184.
337 See DeMets, supra note 184.
338 DeMets, supra note 184.
An important consideration when evaluating early harmful effects should be that the diversity of actions of the therapy under study, and the complex nature of the disease process may produce early harmful effects before the emergence of late, long-term beneficial effects.\textsuperscript{339} In addition, the simple statistical nature of events may cause an early negative trend to be seen which may later reverse itself. While significant large reversals of early trends are uncommon, they have been observed, in particular, in the HERS study and in the ISIS-1 study.\textsuperscript{340} The HERS (Heart and Estrogen/Progestin Replacement Study)\textsuperscript{341} trial assessed the effect of hormone-replacement therapy (HRT) compared with placebo on cardiovascular mortality and morbidity in 2700 women after myocardial infarction.\textsuperscript{342} The DSMB initially observed an almost double increased risk of coronary heart disease in the treatment group; however, after four years of follow-up the risk was found to be equivalent in both groups.\textsuperscript{343} The ISIS-1 (International Study of Infarct Survival)\textsuperscript{344} study of atenolol versus placebo in myocardial infarction demonstrated a complete reversal of an early negative mortality trend.\textsuperscript{345} Early on in the trial, the DSMB noted a negative mortality trend (P value = 0.05) in the atenolol group. Fortunately, the DSMB did not recommend early termination at this time since longer-term follow-up in 16,000 patients showed a significant and clinically important 15% reduction in mortality in the atenolol group.\textsuperscript{346} While reversals such as these are uncommon, caution should be applied to avoid overreacting to emerging negative trends.\textsuperscript{347}

Surgical procedures, as well as other complicated therapies, are particularly challenging to evaluate, as they are often associated with a significant learning curve during their initial implementation.\textsuperscript{348} An example of this can be seen with the Great Ormond Street surgeons in their performance of a new heart surgery on infants who suffer from “transposition of the great arteries,” in which the two main arteries of the heart (the pulmonary artery and the aorta) are switched in their attachments to the heart, a condition that is incompatible with post-natal life.\textsuperscript{349} A prior operation existed (called the Senning procedure) which created a tunnel within the heart to provide blood with a route to the appropriate vessel.\textsuperscript{350} The Senning procedure granted these children a life expectancy into early adulthood, but not old age.\textsuperscript{351} However, in the 1980s, it became technically feasible

\begin{footnotes}
\item[339] See Armstrong, supra note 8.
\item[340] See DeMets, supra note 184.
\item[342] See DeMets, supra note 184.
\item[343] See DeMets, supra note 184.
\item[345] See DeMets, supra note 184.
\item[346] See DeMets, supra note 184.
\item[347] See DeMets, supra note 184.
\item[348] See Armstrong, supra note 8.
\item[350] See Gawande, supra note 349.
\item[351] See Gawande, supra note 349.
\end{footnotes}
to switch the arteries back to their normal positions.\(^{352}\) Unfortunately, in the first 75 of these operations, there was a mortality rate of 25% associated with the new surgery, much greater than the 6% with the Senning procedure.\(^{353}\) However, this new technique was mastered with time (over the next 100 patients) and the mortality rate subsequently dropped to 5% and gave these children a near normal life expectancy.\(^{354}\)

While safety is of paramount importance in DSMB deliberations, other factors will inevitably arise including the “nature, feasibility, cost-effectiveness, and general applicability of the treatment.”\(^{355}\) In some circumstances, a DSMB may find itself in the unusual situation of evaluating a trial in which suffering may be ameliorated at the expense of increased mortality.\(^{356}\) However, in some situations, acquisition of such knowledge may be clinically relevant.\(^{357}\) An example of such a situation can be seen in the PROMISE trial (Prospective Randomised Milrinone Survival Evaluation)\(^{358}\) which was a large multi-center randomized placebo-controlled trial to assess the effect of milrinone on total mortality in patients with moderate to advanced heart failure.\(^{359}\) Interim data analysis for survival steadily approached the boundaries of acceptable harm; however, milrinone is known to improve heart function and exercise capacity and so even a neutral study result would provide useful information.\(^{360}\) Consideration was also given to the fact that patients might have a different risk-benefit profile more accepting of a higher mortality risk if their daily lives were significantly improved.\(^{361}\) For these reasons, the DSMB opted to continue the trial to allow the data to mature; however, if milrinone did not have these other known positive benefits the trial may have been terminated earlier.\(^{362}\) Ultimately, the trial was stopped early due to harm because the data did eventually cross the statistical boundaries for unacceptable harm.\(^{363}\)

While there is little dispute that rapid identification of major treatment advances are extremely important, it is critical to ensure that the study of this treatment yields a valid and definitive result.\(^{364}\) The race to provide new treatments may result in significant tensions between ethical and scientific considerations with regards to the trial process. For this reason, the DSMB is tasked with “recommending early termination on the basis of a positive result only when the data are truly compelling and the risk of a false positive conclusion is acceptably low.”\(^{365}\)

\(^{352}\) See Gawande, supra note 349.
\(^{353}\) See Gawande, supra note 349.
\(^{354}\) See Gawande, supra note 349.
\(^{355}\) Armstrong, supra note 8.
\(^{356}\) See Armstrong, supra note 8.
\(^{357}\) See Armstrong, supra note 8.
\(^{359}\) See DeMets, supra note 184.
\(^{360}\) See DeMets, supra note 184.
\(^{361}\) See DeMets, supra note 184.
\(^{362}\) See DeMets, supra note 184.
\(^{363}\) See DeMets, supra note 184.
\(^{364}\) See FDA, supra note 75.
\(^{365}\) FDA, supra note 75.
10. Conclusion

As should be evident from this paper, the development of mechanisms to protect human subjects in clinical research is an ongoing process. The use of IRBs and DSMBs has made great contributions to the safeguarding of patient welfare and has simultaneously helped to advance the science of medicine. However, as can be seen from the growing criticism of the current nature of IRBs and many of the difficult challenges faced by DSMBs in their decisions to recommend early termination of trials, it should not be surprising that there are still improvements to be made.

With regards to the current nature of IRBs, the Inspector General’s report provides a number of useful recommendations to improve their functioning as discussed above. Unfortunately, implementation of these recommendations would require considerable changes in current federal regulations and would increase the cost and effort required for each research institution. However, in the setting of trials monitored by a DSMB, particularly multi-center trials, a significant savings of IRB resources is possible if the IRB is allowed to cede all continuing monitoring to the DSMB, as the DSMB is already performing that task. This would be particularly useful since IRBs simply don’t have the time or the resources to monitor multi-center clinical trials. In addition, since IRBs typically only have access to adverse event data at their individual institutions under the current system, they have no adequate mechanism to assess those adverse events in the context of the entire trial.

There is a growing body of literature and many federal regulations to help guide the creation, conduct, and ethical foundations of DSMBs. As a result of this growth, it has become well established that the use of DSMBs is very appropriate and beneficial in many scenarios, particularly in trials with major morbidity and mortality endpoints. As is clear from the many examples presented in this paper, many lives have been spared by the intervention of a DSMB. However, DSMBs are not without problems. They add a significant level of cost and complexity to a trial. In addition, overzealous or inexperienced DSMBs can be a danger to the study, particularly in settings where the study is being used to secure regulatory approval of the therapy. It is important that the members of the DSMB have the appropriate statistical background to analyze the data that they receive and the conviction to accept that interim trends (even negative ones) may change with time. The inappropriate early termination of a study can have serious consequences, including potential serious miseducation of the medical community and harm to the patient population. The conviction of DSMB members is particularly important, as they may face significant outside pressures from the media, patient advocates, and pharmaceutical companies to come to a conclusion as quickly as possible.

At this point in time, particularly with FDA providing its own recommendations, it is safe to assume that DSMBs will continue to be established for trials with major morbidity and mortality endpoints. With time and experience, the benefits of DSMB use may extend to trials with less severe outcomes without too much added complexity.
As mentioned earlier, the inappropriate early termination of a trial can have serious negative consequences. What is less often recognized is that appropriate early termination for a negative trend can also have similar negative consequences. This issue was highlighted in the *Publication of Results and Decision Making* section of this paper (section 8.5). Fortunately, significant advances have been made in the past year to help eliminate publication bias, most notably, the effort of the ICMJE member journals requiring trial registration prior to patient enrollment. The ICMJE journal editors should be applauded for confronting this issue with a unified front. However, it is also easily argued that this will result in information overload and that as a result patients, will most certainly not be able to obtain the information they need and deserve from such a database. Only time will tell what impact this requirement will truly have, but it is a noble effort nonetheless. In fact, this effort has already had impact at the federal level; US Senator Charles E. Grassley (R-Iowa) has called on Congress to require the registration of all clinical trials. The importance of proper documentation in clinical research cannot be overemphasized; clinical research depends on the altruism of the involved subjects and there is an ethical obligation to make the results of that research available in return.

In the past year, a major leap forward occurred in the evolution of safety monitoring, bringing patient safety monitoring beyond clinical trials and into the realm of “approved” drugs. This transition is a result of the recognition that real safety testing of a drug does not really occur until it is on the market. A recent article in the New England Journal of Medicine noted that the current “preapproval system is really designed and powered to detect efficacy” rather than safety. This is evidenced by the fact that when a new drug is submitted to FDA for approval, its entire human safety profile is based solely on its effects on the few thousand people who were exposed to it during clinical trials. This is particularly important since rare side effects (those that occur in fewer than 1 in 1000 patients) will generally not be recognized until after the medication is in widespread use. This is a real problem because for certain conditions, the number of patients exposed to the drug may climb into the millions within one to two years on the market.

Unfortunately, FDA’s current postmarketing surveillance system is a passive reporting system, which depends on the efforts of individual “drug companies, health care providers, and consumers.” The system currently registers greater than 375,000 drug-related adverse events per year. However, because these events do not take place in a trial setting, the ability to determine causality is extraordinarily difficult. The current postmarketing surveillance system has also been heavily criticized in particular because it is “unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself.

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367 Okie, supra note 366.
368 See Okie, supra note 366.
369 See Okie, supra note 366.
370 See Okie, supra note 366.
371 See Okie, supra note 366.
wrong." In addition, a number of other flaws with FDA’s current post-marketing surveillance system (MedWatch) have been identified including:

[R]eliance on voluntary reporting of adverse events by physicians and other health care professionals; poor quality of submitted reports, often with inadequate documentation and detail; underreporting of adverse outcomes resulting in capture of only a small fraction of adverse events that actually occur; difficulty in calculating rates of adverse events because of incomplete numerator data on events, coupled with unreliable denominator data on exposure; limited ability for spontaneous reports to establish causal relationships; and difficulty in determining whether the adverse event resulted from the drug or the disease it was intended to treat.  

These problems are well recognized at FDA; in particular, deputy FDA commissioner Janet Woodcock noted “given how many people are exposed to drugs, how quickly they’re taken up in the population, how many people take multiple drugs … we’re under no illusions that we have a good postmarket system right now.” For these reasons, some authors have suggested decoupling the drug approval process from the post-marketing safety and surveillance system by establishing an independent drug safety board or an independent agency for drug safety, specifically to oversee postmarketing surveillance for drugs and devices. 

As a result of the strong opinions expressed that FDA does not do enough to monitor drugs already on the market, FDA announced on February 15, 2005 that it will create a “new independent Drug Safety Oversight Board to oversee the management of drug safety issues, and will provide emerging information to health providers and patients about the risks and benefits of medicines.” As part of this task, FDA will analyze large managed-care databases to help assess the benefits and risks of medications currently on the market. This clearly marks the next step in the evolution of safety monitoring in clinical research. However, this new board has already been criticized for being composed of FDA officials and medical experts from other HHS agencies, despite having a declaration of independence. While FDA’s ability to establish an independent and impartial safety monitoring board may be in question, if it does manage to function as advertised, physicians and patients may be able to “review the evidence, listen to the debate, and judge for themselves.” This would truly be a significant benefit both for

374 Fontanarosa, supra note 373.
375 Okie, supra note 366.
376 See Fontanarosa, supra note 373.
379 See Harris, supra note 378.
380 Okie, supra note 366.
society and for those conducting clinical research. It could provide a measure of protection for sponsors against unwarranted litigation, a greater sense of trust among the volunteer patient population, and a significant reduction in unnecessary harm to patients as a whole.

In summary, there has been significant growth over the past half-century in measures to protect human subjects involved in clinical research. The Nuremberg Trials in the 1940s and growing media attention to clinical research abuses in the 1960s provided the necessary initial catalysts to spur widespread action to protect human subjects. Since then, the mechanisms to provide such protections have undergone considerable evolution and are part of standard practice today. As a result of the benefits to both patients and researchers, the evolution of patient safety monitoring is continuing into the postmarket arena where despite being “approved,” drug use could still be called continuing research. Hopefully, FDA will take advantage of growing literature regarding patient safety monitoring that has grown out of the use of IRBs and DSMBs and will utilize that knowledge to implement an active and successful postmarketing safety monitoring system.
Appendix

A. The Nuremberg Code (1946)\textsuperscript{381}

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects.

PERMISSIBLE MEDICAL EXPERIMENTS

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility, which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

\textsuperscript{381} Available online at: http://ohsr.od.nih.gov/guidelines/nuremberg.html (April 2005).
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

B. Declaration of Helsinki (1964)\textsuperscript{382}

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. 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.

\textsuperscript{382} Available online at: http://www.wma.net/e/policy/b3.htm (April 2005).
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in
accordance with the principles laid down in this Declaration should not be accepted for publication.

J. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

1. Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.