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Introduction

The ASSERT statement represents a declaration and elaboration of the necessary requirements for the ethical conduct of human subjects research in the form of randomized controlled clinical trials. It serves both as an explication of scientific and ethical precepts constitutive of the proper conduct of clinical research and, in particular, a proposal intended to operationalize these precepts in the context of review of proposals for trials by research ethics committees. The latter aspect is effected through the formulation of a checklist of items to be addressed in formal applications for research, and systematically evaluated by research ethics committees.

The checklist encompassed within the table below contains informational items pertinent to each of the five sections to be addressed in the Application for Research. Hyperlinked items in the *description* sections will direct the reader to separate pages wherein elaboration is provided. Some of the hyperlinks will take the reader to pages on the CONSORT Web site, where specific examples and elaboration will be found. Each linked page will open in a new browser window −− close this window to return to the checklist.

Checklist of sections and items to include in an application for research

APPLICATION SECTION	ITEM	DESCRIPTION
SOCIAL AND SCIENTIFIC VALUE Background	1	Exposition of scientific background, rationale and relevance. This should be referenced to a Systematic Review whenever feasible.
Trial registration	2	Details about trial registration and International Standard Randomised Controlled Trial Number (ISRCTN)
Public dissemination of trial results	3	Plans for public dissemination of results; name/s and affiliation of individuals responsible for results dissemination, including contact information.
SCIENTIFIC VALIDITY (items 4−12 are from the CONSORT statement) Participants	4	Eligibility criteria for participants.

Objectives	5	Specific objectives and hypotheses
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, methods used to enhance the quality of measurements
Sample size	7	How sample size was determined
Randomization −− Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).
Randomization −− Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Randomization −− Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.
FAIR SUBJECT SELECTION Recruitment of participants	13	Description of the populations from which participants will be recruited, including details concerning location, age groups, gender, ethnicity and whether participants will be recruited from vulnerable groups.
FAVORABLE RISK−BENEFIT RATIO Interventions offering the prospect of health−related benefit	14	Ordered enumeration and explication of research interventions offering the prospect of direct health−related benefits
Interventions performed solely to answer the research question	15	Ordered enumeration and justification of interventions (invasive; measurement; data collection; surveys, etc.) performed solely to answer the research question and generate generalizable knowledge.
Clinical equipoise	16	Description and justification of control and experimental arms, including modes and dosages of drug administration. Reference the claim of clinical equipoise to an applicable

		Systematic Review whenever pertinent.
RESPECT FOR POTENTIAL AND ENROLLED SUBJECTS Trial monitoring plan	17	Description and justification of a formal trial monitoring (safety and efficacy) plan. Details concerning a DSMB (if applicable), including names/affiliations of members and details concerning the stopping guidelines for the trial, and how they were chosen.
Communication of protocol changes and trial monitoring results	18	Details concerning the method and timing of transmission of protocol changes and trial monitoring results to research ethics committees.

Research Ethics Committees should incorporate this checklist in their Applications for Research, and reference this Web site in the application to assist investigators in complying with ASSERT's requirements.

Comments

Applicants for research approval should use this checklist to ensure that all the associated items are addressed in the Application for Research. Commercial sponsors of drug trials typically provide investigators with an *Investigators Brochure* in compliance with *Good Clinical Practice* (1), the latter formulated by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (2), for use in drug trials. While the brochure may address certain aspects of the checklist items in a limited fashion, it is not a substitute. The checklist items may be considered constitutive of a Protocol Summary for distribution to members of the research ethics committee evaluating the trial application.

In multicenter trials, local research ethics committees are unable to influence the design of a trial submitted for review by local investigators, the latter having been recruited to participate by the trial's Steering Committee or a contracted third party . The committee may request amendments or changes to the submitted Informed Consent document, but actual approval is reduced to a take−it−or−leave−it proposition. By endorsing the ASSERT statement, and considering only applications that are in conformity with its itemized requirements, committees will help assure the ethical conduct of research.

Research ethics committees have been criticized for not paying sufficient attention to the relevance of the research they approve; ensuring that clinical equipoise is present at trial inception; and ensuring the public dissemination of the results of the trials they approve (3). By endorsing the ASSERT statement and conducting continuing review of the research until the trial's results are reported, committees will be positioned to respond to such concerns.

Funding agencies may also stipulate provision of pertinent checklist items in applications for research funding. Such agencies have an obvious interest in ensuring the responsible use of limited financial resources. In particular, the requirement for scientific and social value is relevant to such agencies.

Because the checklist represents a structured approach to the ethical conduct of research, it may also be used as an evidence−based research tool to determine whether compliance with

the ASSERT statement results in improvements in the conduct and reporting of trials. Authors of manuscripts submitted for publication should be encouraged to report whether the trial was approved by a research ethics committee, and whether it was conducted in conformity with the ASSERT statement. This will enable researchers to determine whether this leads to a verifiable improvement in associated parameters such as the assurance of clinical equipoise at trial inception; the publication of trial results, whether positive or negative; and the reporting of results in conformity with the CONSORT statement.

References

References available online are hyperlinked.

1. Good Clinical Practice. International Conference on Harmonization. Investigator's Brochure.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

3. Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. BMJ 1996; 313:1390−1393.

Scientific background, rationale and relevance

> *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*
>
> ***Declaration of Helsinki. Principle 11***

The conduct of a controlled clinical trial is ethical if it will contribute valuable and relevant knowledge that promotes health and well−being (1). Clinical trials encompass a wide range of objectives, which must be of scientific and social value to be deemed ethical. Examples include trials evaluating the efficacy and safety of investigational drugs (compared with an active control or placebo), typically used to support an application for regulatory approval for marketing purposes (2); trials comparing the relative efficacy and safety of approved therapeutic agents or interventions; trials performed to acquire additional or more pursuasive data when substantial doubt exists concerning the net therapeutic effectiveness of an approved drug or commonly applied intervention. The ***notion of social value*** necessitates judgments on the part of all members of the committee −− those with and without scientific expertise in the field of research under consideration. The research question must be meaningful in that the results should help resolve an issue of substantial clinical import to patients and communities. Furthermore, communities from which the participants are recruited should be judged able to utilize or implement the knowledge gained. In this respect, health−care consumers and policymakers involved in the allocation of health−care resources have an important potential role in determining the salience of proposed trials. Trials that propose to evaluate clinically trivial treatment effects may be judged unethical. This *background* section of the research application should address these issues in a manner comprehensible to those without specialized scientific knowledge of the clinical issues under consideration.

The ***notion of scientific relevance*** is equally important, and connotes an assessment of the trial's objective in light of existent knowledge. The latter may be voluminous or scanty. The evidentiary quality of existing knowledge exists on a continuum from questionable to pursuasive, and is incorporated, for example, in formal measures of trial quality (3). Hence, the relevance of a proposed trial must be considered in relation to a comprehensive assessment of both the quantity and validity of existent knowledge. In addition, the proposed trial should not (absent substantial scientific justification) duplicate or substantially overlap other completed or ongoing trials. Inadequate knowledge of the results of completed trials may lead to the choice of a clinically inappropriate control arm (4). These factors necessitate and justify a requirement that relevance be referenced, whenever possible given the nature of the trial proposed, to a current Systematic Review of the pertinent literature.

As noted by Emanuel et al. (5), there are two fundamental reasons why scientific and social value (and relevance) should be considered an ethical requirement: responsible use of limited societal resources and avoidance of exploitation. The latter invokes the notion of exposing research participants to possible harm without the potential for acquiring valuable and relevant knowledge.

Systematic Reviews and assessment of value and relevance

As declared in principle eleven of the Declaration of Helsinki reproduced above, the conception and design of a clinical trial should be informed by a "...thorough knowledge of the scientific literature..." In recognition of the large volume and varying quality of the published reports of clinical trials associated with almost any important clinical issue, the necessity and utility of referencing a proposed trial to a pertinent Systematic Review are compelling. Assessing the objective of a

proposed trial in relation to the results of a Systematic Review will enable a determination of relevance, avoidance of duplication of previously conducted trials, and inappropriate exposure of participants to interventions known to lack net therapeutic efficacy. Conversely, a Systematic Review may support the conduct of a trial by confirming the scientific need for replication of a previously conducted study. These, and other, reasons for referencing a proposed trial to a Systematic Review have been explicated by Chalmers (6), and are summarized in the table below. Further elaboration is found in other sections of this document.

Utility of Systematic Review in assessing a proposed trial
Assessment of clinical value and relevance
Assurance of clinical equipoise
Assessment of significance of interim results analysis
Contextual reporting of results

The application for research may reference an existent up−to−date Systematic Review such as may be found in the Cochrane Library (7), or provide a review performed by an investigator involved in the trial. If, due to the novel nature of the trial's subject matter, a Systematic Review is not pertinent, the primary investigator should clarify this in the application.

Growing recognition of the relevance of referencing Systematic Reviews in proposals for clinical trials is evidenced in statements by agencies such as the European Science Foundation (8), and funding agencies such as the U.K.'s Medical Research Council (9).

References

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1. Declaration of Helsinki. Principle 6.

2. F.D.A. Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. 1998.

3. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized trials: is blinding necessary? *Control Clin Trials* 1996; 17:1−12.

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5. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000; 283:2701−2717

6. Chalmers I. Using systematic reviews and registers of ongoing trials for scientific and ethical trial

design, monitoring, and reporting. In, Egger M, Davey SG, Altman DG (editors) *Systematic Reviews in Health Care: Meta−analysis in Context*. London. BMJ Books. 2001, pp 429−443.

7. The Cochrane Library

8. European Science Policy Briefing No.13. Controlled Clinical Trials.

9. U.K. Medical Research Council. Proforma for funding applications for controlled trials.

Scientific validity

> *Medical research involving human subjects must conform to generally accepted scientific principles.*
>
> ***Declaration of Helsinki. Principle 11***

Research that is not conducted in conformity with valid scientific principles cannot produce relevant results. Indeed, such results may be misleading and contribute directly, and indirectly, to harmful clinical practices. Exposure of human participants to the risks and burdens of such research is unethical.

The notion of social value presupposes scientific validity (1). Research ethics committees have been criticized for paying insufficient attention to the "methodological rigor in proposals presented for their attention."(2) In a published editorial entitled *The scandal of poor medical research*, Altman (3) also alludes to the inadequate review of the methodological aspects of research proposals by research ethics committees. Committees may not have members with the necessary expertise in the proposed research to make the necessary assessment concerning scientific validity. In addition, committees traditionally spend an inordinate amount of time parsing the informed consent document, and relatively little or no attention to the scientific aspects of the research proposal. Freedman and Shapiro (4) have commented on the tendency of research ethics committees to neglect design issues in clinical trials, thus overlooking many items (such as eligibility criteria and statistical considerations) pertinent to an assurance that the proposal meets the requirement of scientific validity and relevance. Unfortunately, in the case of multicenter trials, a local research ethics committee is not in a position to affect the design of the research protocol, and its consideration takes on the character of a take−it−or−leave−it proposition. In other cases, the erroneous assumption is often made that a particular proposal has undergone careful *and credible* scrutiny by a scientific merit, or like, committee. While such institutional committees exist, their ability to adequately assess the scientific validity of research proposals is unknown. Details concerning the nature and structure of such reviews, and the deliberations of such committees, are not generally made available to research ethics committees.

In response to these current limitations, local research ethics committees should adopt a standard for the design and reporting of clinical trials that will ensure that proposals meet the requirement of scientific validity. The nature and scope of such a standard is elucidated in the following sections.

Scientific validity and randomized controlled clinical trials

The assessment of scientific validity with respect to randomized controlled clinical trials invokes notions of *internal* and *external validity*. Internal validity represents the extent to which systematic error (bias) is minimized in clinical trials, and external validity the extent to which the results of trials provide a correct basis for generalization to other clinical circumstances (5). This article by Juni et al. also explicates the nature of biases that may adversely affect internal validity: selection; performance; detection; and attrition biases. An assessment of generalizability requires attention to specific factors such as the clinical status of trial participants; details concerning the therapeutic components in the trial; the settings in which such components are administered; and the nature of the outcomes measured and duration of clinical follow−up. A systematic evaluation of these items is necessary to make a general judgment of the trial's quality, and hence its value.

Fortunately, a pre−inception assessment of a trial's scientific validity is greatly facilitated by the CONSORT statement (6). The CONSORT Working Group has identified and elaborated on specific items that should be addressed by the designers of the trial to ensure internal, and to promote

external, validity. The identification of such items is supported by empirical evidence of bias in the conduct and reporting of trials, fully referenced in the CONSORT's elaboration document (7).

This section of the ASSERT checklist is thus comprised of specific items in the CONSORT checklist relevant to a determination of scientific validity. The associated principles and logic should be familiar to research ethics committee members. Trial designers and investigators responsible for the reporting of the trial's results should address these items in the Application for Research. By doing so, they will be able to correct flaws in the research design before the inception of research−related activities, and will be prepared to report the results of the trial in an appropriate manner.

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5. Jüni P, Altman DG, Egger M. Systematic reviews in health care. Assessing the quality of controlled clinical trials. *BMJ* 2001;323: 42−46.

6. The CONSORT statement.

7. The CONSORT elaboration document.

Trial Registration

The design of all studies should be publicly available

Declaration of Helsinki. Principle 16

Biomedical research is a public endeavor, intended primarily to produce scientific knowledge to be used to promote health and well−being. The cost of research is funded, directly or indirectly, by the public. The public's health is best promoted when research is conducted in a manner that permits continuing scrutiny and appraisal by lay and expert citizens.

Calls for trial registration have been made by journal editors (1), funding agencies (2), and others (3,4) seeking to improve the scientific and social value of clinical trials. Registers diminish publication bias by exposing under−reporting of trial results; prevent duplication; promote collaboration; and directly serve physicians and patients by making information about available trials readily accessible. A comprehensive summary of the reasons why trials should be registered has been published by Tonks (5), and is adapted and reproduced in the table below.

Why register trials?
To mitigate against publication bias − the underreporting of trials with disappointing, negative, or inconclusive results − which misleads researchers conducting systematic reviews and doctors making decisions based on published evidence
To prevent unnecessary duplication of research effort, while encouraging appropriate replication and confirmation of results
To alert researchers to gaps in the knowledge base
To foster international collaboration among researchers and stimulate recruitment to clinical trials, enhancing their chances of success
To provide reliable intelligence about ongoing trials that will help funding bodies target their money where it is most needed
To aid recruitment to trials by direct appeal to the public
To provide a searchable database of current research efforts
To improve accessibility and therefore credibility of research performed by the pharmaceutical industry
To satisfy public demand for unbiased evidence on the effectiveness of treatments, and to promote the public accountability of medical research in general

Journals are increasingly likely to require evidence of trial registration before a manuscript reporting trial results is considered eligible for publication. The *Lancet* has instituted a program (6) whereby it will review trial protocols before the inception of research in anticipation of eventual publication of the results in the journal. This consideration is contingent on trial registration.

Many trial registers exist. Some register trials in all areas of medicine, while others are restricted to speciality areas. To promote ease of access and efficiency in searching for relevant trials, cooperation between registers and centralization is necessary. Electronic links between registers, trial−related Web sites and online Systematic Reviews is necessary. A searchable meta−register of trials may provide essential details concerning a trial, with a link to a trial−related Web site wherein additional information of relevance to researchers and research ethics committees is provided.

At present, trial registration is generally voluntary. In the U.S., the Food and Drug Modernization Act of 1997 (7) mandates the submission of information to a Clinical Trials Database for drug studies involving "serious and life−threatening diseases," and the F.D.A. recently issued draft guidance on this requirement (8). In addition, the F.D.A. has proposed the mandatory submission of clinical trial information for research involving gene transfer and xenotransplantation (9). This is an important, but limited step, in the right direction. Research ethics committees should require evidence of trial registration for *all* controlled clinical trials, irrespective of the nature of the research, in service of the requirement for scientific and social value.

International Standard Randomised Controlled Trial Number

The concept of trial registration will work best with a centralized, coordinated Internet−based registration system. A large number of trial registers already exist, generally organized around specific disease entities. Such dispersal is best avoided in favor of a centralized database of trials, the latter facilitating efficient and reliable electronic searching by interested parties.

To facilitate the recognition of trial registration, each trial should acquire an International Standard Randomised Controlled Trial Number (ISRCTN). This number is assigned to trials registered at *Current Controlled Trials*, which maintains a searchable meta−register of trials. Each registered trial may be associated with an external link to a specialized trial register or a Web page wherein additional information about the trial is provided. The number will greatly facilitate tracking of clinical trials and associated reports worldwide, and may be electronically linked to repositories of Systematic Reviews concerning the clinical issue under investigation. Research Ethics Committees should support this effort to establish a centralized registration system given the international scope of performance of clinical trials.

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2. Medical Research Council (U.K.)

3. Chalmers I. Current Controlled trials: an opportunity to help improve the quality of clinical research. *Curr Control Trials Cardiovasc Med* 2000; 1:3−8.

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7. FDA Modernization Act of 1997. CDER−Related Documents.

8. Guidance for Industry. Information Program on Clinical Trials for Serious or Life−Threatening Diseases: Establishment of a Data Bank. 2001.

9. Human gene therapy or xenotransplantation; data and information disclosure. *Federal Register*. January 18, 2001.

Public dissemination of trial results

> *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*
>
> ***Declaration of Helsinki. Principle 27***

A research activity involving human subjects is complete when its results are released into the public domain. There are a number of inter−related imperatives for the public dissemination of the results of clinical trials:

A judgment that the nature of the proposed research meets the requirement of scientific and social value presupposes that the research results will be publicly disseminated. This is analogous to the notion that the requirement of scientific and social value cannot be fulfilled if the research design is not scientifically (internally) valid. (1).

Research on human subjects typically includes interventions that offer the prospect of health−related benefits, and interventions performed solely to answer the research question. This is invariably the case in clinical trials. While the risks associated with therapeutic interventions may be justified on the basis of anticipated health−related benefits, the risks (demarcated research risk) associated with non−therapeutic interventions are justified solely by the prospect of acquiring valuable and relevant knowledge (2). This distinction is elaborated upon more fully in a separate section of this statement. Failure to publish the acquired knowledge renders the exposure of research participants to demarcated research risks ethically unjustifiable.

Failure to disseminate research results, positive or negative, adversely affects the relevance of published results of other trials and the utility of Systematic Reviews and Meta−analyses of trials (publication bias). Failure to publish negative results may expose future patient−subjects in trials to interventions known to be inferior to other currently utilized treatments (3).

Empirical research (4) evaluating reasons why patients agree to participate in clinical research, including trials, has revealed that patients are primarily motivated by two factors: the anticipation of health−related benefits, and an expression of trust in the physician proposing research participation. A third motivation is an altruistic one −− the hope that future patients will benefit from the knowledge gained −− and the failure to publish the research results dishonors such principled volunteerism.

The research participants, whose enrollment made the clinical trial possible, are entitled to know the results of the trial, and the implications for their health.

The duty to share new knowledge with colleagues is a longstanding norm in the medical profession, commonly enunciated in professional codes of conduct. This imperative applies also to the acquisition of knowledge by a physician engaged as an investigator in clinical trials. These notions are summarized in the table below.

Ethical imperatives for the public dissemination of research

results
A judgment that the research meets the requirement of scientific and social value presupposes the public dissemination of results
Justification for the inclusion of non−therapeutic interventions designed to answer the research question
Avoidance of publication bias, which adversely affects clinical decision− making and the utility of Systematic Reviews and Meta−analyses of the published literature
Honors the altruistic motivations of patient−subjects who agree to participate in a clinical trial
Participants are entitled to know the results of the research their enrollment made possible
Dissemination is consistent with the duty to share new knowledge with colleagues, commonly found in professional codes of conduct

In recognition of these imperatives, research ethics committees should ascertain the nature of plans to disseminate research results in a timely manner after completion of the trial. Full publication of results in peer−reviewed print and online journals should be the primary means of results dissemination. Results of clinical trials are often presented initially in the form of abstracts or short reports at medical conferences. Scherer (5) has reported an analysis of 46 studies describing subsequent full reporting of studies initially presented in abstract or short−form, showing an average rate of full publication of 44.8%. The utility of such reports is limited, particularly with respect to an assessment of the trial's internal and external validity, and the inability to incorporate the results of these trials in Systematic Reviews or Meta−analyses of the pertinent clinical literature. Thus, only full reports of trials should be considered an acceptable form of results dissemination. Investigators should be made aware of the CONSORT statement (6) regarding the appropriate reporting of trial results. Alternative forms of results dissemination may be the submission of results to established Trial Banks(7), or publication on a Web page which is linked to an established trial register. The last is least desirable, but the advent of the Internet makes dissemination of all results feasible. Investigators should also be encouraged to make the patient−level (raw) data accumulated during the trial publicly available at an appropriate time. This is a notion worthy of more debate.

Ascertainment of the dissemination of results

Research ethics committees typically have oversight obligations during the ongoing conduct of research− related activities. For example, in the U.S., federal regulations specify the need for continuing review and re−approval of research at intervals not exceeding one year (8). In general, trial completion is considered to be the point at which all trial−related interventions have been completed in all participants. However, a more meaningful concept is that trial completion coincides with the public availability of the research results, which may then be integrated into the corpus of existent knowledge.

To assure the dissemination of research results, particularly the reporting of the pre−specified primary and secondary outcome measures, committees should conduct continuing review until these results are reported as described above. To this end, the application for research should provide the name of the investigator, with contact

information, assuming responsibility for the public dissemination of the research results. In the case of multicenter trials, the names and affiliations of members of the trial's Publication Committee should be provided. These investigators should be encouraged to provide updated information concerning the publication of trial results on a trial−related Web site as described elsewhere in this statement. This will enable the committee to determine the progress towards results dissemination with minimal effort.

Failure to report research results should be considered a form of research misconduct (9). Research ethics committees should ascertain whether the investigators who assumed responsibility for results dissemination are culpable. Committees need to ascertain whether investigators proposing to conduct human subjects research are qualified to do so, and failure to disseminate research results bears directly on this issue. Such failure is a proper consideration when the investigators submit new research proposals for review. Unfortunately, such considerations are necessary in the current research environment wherein financial conflicts of interest and questionable industry−investigator alliances not uncommonly culminate in attempts to suppress the dissemination of unfavorable research results (10−13).

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6. The CONSORT statement.

7 Sim I, Owens DK, Lavori PW, Rennels GD. Electronic trial banks: A complementary method for reporting randomized trials. *Medical Decision Making.*2000; 20:440−450.

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13. Gottlieb S. Firm tried to block report on failure of AIDS vaccine. *BMJ* 2000; 321:1173.

Fair Subject Selection

> *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.*
>
> ***Declaration of Helsinki. Principle 8***

This requirement for the ethical conduct of research concerns the strategy whereby research participants will be recruited. Generalizability of research results to the population at large depends, in part, on the appropriate choice of eligibility criteria, the latter declared in the section addressing the requirement of scientific validity. Once eligibility criteria are formulated, recruitment should not be restricted to certain populations of potential participants simply on the basis of convenience or efficiency, or by exploiting vulnerable individuals or communities. Many possible vulnerabilities may be identified: cognitive (including impaired decisional capacity); deferential; institutional; social; economic; and medical. Because clinical trials are often international in scope, research ethics committees in each country involved should evaluate proposed recruitment practices in its local and regional communities, mindful that the aforementioned vulnerabilities are inherently contextual, and will vary across regional and national boundaries.

Research ethics committees should also evaluate whether there will be an equitable distribution of potential benefits and burdens −− those who bear the potential risks of the trial, and the communities from which they are drawn, should not be systematically excluded from realizing the potential benefits of the research. The presence of clinical equipoise (1) at the inception of the trial ensures that potential participants are not disadvantaged by participating, but meaningful benefits may depend on continued access to the drug or intervention after completion of the trial. In addition, the judgment of clinical equipoise at the inception of the trial may be difficult, and contentious, when research is conducted in poor, developing nations by researchers from wealthy, industrialized countries. The interventions studied may not ordinarily be available in the countries concerned. This also bears on the notion of social value, a separate requirement for the ethical conduct of research. A full discussion of this important consideration is beyond the scope of this document, and the reader is referred to reports issued by the National Bioethics Advisory Commission in the U.S. (2), and the Nuffield Council on Bioethics in the U.K. (3), for additional elaboration.

The applicable notion of (distributive) justice is also elaborated on in the Belmont Report (4) which guides the deliberations of Institutional Review Boards in the U.S. The report also discusses two other ethical principles applicable to human subjects research: beneficence, and respect for persons.

Individuals from specific groups, such as women, should not be inappropriately excluded from the potential benefits of clinical trial participation. Such exclusion has traditionally arisen from concerns about the possible teratogenic effects of investigational agents, but is no longer considered justifiable (5). Similarly, the presence of clinical equipoise permits the ethical enrollment of children in clinical trials. Because drugs are typically utilized "off−label" in the pediatric population (6), appropriately conducted controlled trials in this age group are indispensible.

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Favorable risk−benefit ratio

> *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.*
>
> ***Declaration of Helsinki. Principle 16***

Research in the form of controlled clinical trials involves components that offer the prospect of direct health−related benefits (therapeutic components), and components that are included solely to answer the research question (non−therapeutic components). The research question is typically framed in the form of a null hypothesis that states that there is no difference between the trial arms with respect to the outcomes measured. These non−therapeutic components may take the form of invasive or non−invasive diagnostic and prognostic testing procedures, not ordinarily performed in the course of clinical care; accumulation of additional clinical and biochemical parameters; performance of investigational genetic tests on blood or tissue samples as ancillary research studies; and a greater intensity or duration of follow−up monitoring after the completion of the therapeutic interventions.

As with other forms of research, the design of the research protocol should maximize benefits and minimize risks to research participants. Research ethics committees should engage in a systematic, non−arbitrary assessment of risks and benefits associated with the clinical protocol insofar as possible (1). To this end, a systematic, component−based approach to risk−benefit assessment proposed by Weijer (2) is recommended for this section. This approach makes a clear distinction between the research components described above, and emphasizes that the associated risks and benefits should be considered separately −− risks associated with non−therapeutic components cannot be justified on the basis of the potential benefits derivative of the therapeutic components. This notion is discussed further in the sections that follow.

Interventions offering the prospect of health−related benefits

The therapeutic components are directed towards the participant as a patient. Risks associated with therapeutic components are justified by the prospect of health−related benefits (a risk−benefit calculus). Such risks are assumed by patients receiving therapeutic interventions outside of the trial setting, and this concept is generally well understood by doctors and patients. In general, it is recognized that informed patients may assume greater risks (considering both probability and magnitude) in return for the prospect of benefits they judge worthwhile. In the trial setting (assuming the presence of clinical equipoise as discussed below), the situation is conceptually analogous. The patient−subject, fully apprised of the possible risks and benefits associated with the therapeutic interventions in both arms, may then make a personal judgment with respect to trial participation.

Interventions and evaluations performed solely to answer the research question

The non−therapeutic components are experienced by the participant as a research volunteer. Risks associated with non−therapeutic components (also referred to as "demarcated research risk") are justified by the prospect of acquiring valuable and relevant knowledge (a risk−knowledge calculus). The knowledge gained is intended primarily to benefit future patients. Research ethics committees, comprising members with the necessary scientific and non−scientific expertise to evaluate the proposed trial, should make a determination that the inclusion of such interventions is scientifically necessary in relation to the methodologic and statistical aspects of the trial design, and justified in

relation to the value and relevance of the knowledge to be gained.

When research involves vulnerable participants such as children or individuals with impaired decisional capacity, regulations or guidelines may specify that the risks associated with research participation be limited to *minimal risk* (3) or a *minor increase over minimal risk*. An example of this is the regulatory prescription of permissible categories of research involving children in the U.S. as codified in Subpart D of the *Common Rule* (4), and also formally adopted by the F.D.A. Considering the component−based approach to risk analysis, these risk limitations should be applied to the non−therapeutic research components. Thus, the need to identify and distinguish between therapeutic and non−therapeutic components is evident, and should be delineated as such in the application for research.

Establishment of clinical equipoise

> *The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.*
>
> ***Declaration of Helsinki. Principle 29***

Randomized controlled trials are performed to accomplish this purpose, and may also be used to evaluate the comparative efficacy of currently available and utilized treatments. Stated differently, a randomized trial is performed to resolve uncertainty about the efficacy of an intervention, particularly when considered in relation to other available treatments, if any (5). At the inception of a randomized trial, there should be genuine uncertainty concerning which arm of the trial may be superior, when both benefits and risks associated with the interventions are taken into account. This notion has been termed the *uncertainty principle*, and may be present at three levels as described by Rolleston (6) and Sackett (7). The latter's elaboration is adapted and summarized in the table below.

Levels of uncertainty relevant to the conduct of, and participation in, a randomized controlled clinical trial
Community uncertainty −− reflecting the collective judgment of the community of expert practitioners in the pertinent field, and derivative of a systematic assessment of existent evidence in the medical literature
Individual clinician uncertainty −− reflected in the opinion of an individual practitioner who needs to decide whether to recommend participation to a particular patient
Patient uncertainty −− as expressed through the patient−physician relationship, and representing a patient's values derivative of an informed consideration of purported benefits and risks of available treatments

The notion of *community uncertainty* is particularly relevant to research ethics committees which must decide whether to approve the proposed trial and thus make it available to potential participants. This level of uncertainty represents the moral underpinning of randomized clinical

trials, and is the state of *clinical equipoise* as originally conceived by Freedman (8). *Equipoise* implies that the expected size and probability of improvement balance the size and probability of side effects (perceived risks) of comparator treatments (9). This concept is perhaps less ambiguous than the notion of uncertainty. More recently, Weijer and colleagues (10) have again emphasized the relevance of clinical equipoise over the uncertainty experienced by the individual clinician as a precondition for trial inception. The presence of clinical equipoise permits the simultaneous accomplishment of two objectives: offering the patient−participant the best bet (in the presence of uncertainty) of getting the best treatment through the process of randomization, and acquiring valuable and relevant medical knowledge.

Investigators proposing a trial should provide the committee with relevant background information in support of a claim of equipoise, including reference to a pertinent Systematic Review (11) whenever feasible. If a Systematic Review is not available for the subject under investigation, the investigator should provide the committee with details concerning the literature review conducted in support of the conduct of a randomized controlled trial. These details should include a full description of the methods and search strategy utilized to acquire and synthesize the relevant medical literature. Guidance in this regard is available from the Cochrane Collaboration (12).

A systematic literature review will also serve to accumulate evidence in support the choice of a control arm, particularly when new therapies are being evaluated. It has been demonstrated in analysis of reported trials that inappropriate choices have been made, particularly when trials are supported by commercial sponsors (13). Analogously, the use of placebo controls must be carefully appraised to ensure that clinical equipoise is present. If equipoise is not present, the use of a placebo control must be explicitly justified. The use of placebo controls is a contentious issue (14), and a full discussion is beyond the scope of this document.

With respect to a particular trial, a physician may or may not be in equipoise. In recognition of his fiduciary status derivative of the physician−patient relationship, he may be uncertain whether to offer participation to his patient. Even if he is not in equipoise, he should inform his patient of the availability of a trial, thus fulfilling the obligation to provide information concerning alternatives to any proposed treatments. Indeed, it has been proposed that this is a moral requirement (15). Analogously, the potential participant should be provided all the necessary information about the trial so that the patient, expressive of his personal medical goals and values, may determine whether he is in equipoise and thus willing to undergo randomization.

The concept of component−based risk analysis, and the application of clinical equipoise to the analysis of a clinical research protocol is summarized in this figure from Weijer, which is reproduced with the permission of the author.

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Monitoring the conduct of a trial

> *The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events*
>
> ***Declaration of Helsinki. Principle 13***

According to Emanuel and colleagues (1), respect for potential and enrolled subjects comprises five elements: respecting participants' informational privacy interests; permitting participants to withdraw from the trial without penalty; providing enrolled participants with any new information that may affect their willingness to remain in the trial; monitoring participants' safety, particularly with respect to the occurrence of adverse events; and providing participants information about the outcome of the trial.

The checklist addresses two items that are necessary to fulfill this requirement for the ethical conduct of research: the trial monitoring plan and the means whereby the results of such monitoring will be made readily available to research ethics committees. Committees have obligations towards participants that are encompassed in the notion of *continuing review* (2), which is particularly important during the time participants are being recruited, research−related interventions are being applied, and interim results are collected and analyzed.

Because controlled trials typically involve multiple centers, each of which may recruit only a few participants, research ethics committees may not be able to acquire a contextually meaningful sense of the overall experience of trial participants. In industry−sponsored trials, committees may receive a large volume of unaggregated adverse event reports emanating from other centers, but be unable to determine their significance. Morse and colleagues (3) have reported on the deliberations of a group of professionals with expertise in various aspects of clinical trials, confirming the challenges committees face in the context of multicenter trials. They describe certain actions and requirements that should be fulfilled by the various parties involved in clinical trials, which are adapted and summarized in the following table.

Actions and requirements for clinical trial monitoring
A formal, systematic plan is required for each trial.
The plan must be included in the application for research and approved by the research ethics committee.
The plan should provide for the provision of aggregated data summaries, and an explanation of the severity and relatedness of adverse events to the trial interventions, to research ethics committees at pre−specified intervals.
Independent Data and Safety Monitoring Committees (DSMB) should be constituted when applicable. The means whereby summaries of its deliberations will be provided to research ethics committees at regular intervals must be declared.
A summary of the DSMB's governance structure, and its operational and statistical approach to interim results analysis, should be pre−specified and elaborated on in the research application

The trial monitoring plan

The complexity and intensity of safety monitoring should be proportionate to the potential risks, and the number of participants and centers involved in the trial. Small, single−institutional trials in which anticipated risks associated with the trial−related interventions are limited (severity and frequency) may necessitate only a monitoring group consisting of the primary investigator, a statistician, and an individual independent of the trial, such as a member of the research ethics committee. The plan should declare when interval reports of aggregated data will be provided to the committee. This may be related to specified time intervals or the number of subjects enrolled.

In the U.S., the F.D.A. requires the submission of *Annual Reports* from sponsors of drug trials conducted under an IND (Investigational New Drug) application (4). The reports must include summary information such as the number of subjects enrolled to date; the number of subjects withdrawn from the trial; a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system; a list of subjects who died during the reporting interval, with the cause of death; and a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

For trials conducted under an IND, the monitoring plan should include a provision for transmittal of this annual report, or equivalent report, to the committee at pre−specified intervals.

Establishment of a Data and Safety Monitoring Board

Because controlled trials vary substantially in nature and scope, there are no definitive indications for establishment of a DSMB. Factors that should be considered when deciding on the potential applicability for interim results monitoring include the nature of the outcomes evaluated; the likely temporal relationship between the occurrence of measured outcomes and the estimated time period during which subjects will be accrued for the trial; and the nature of the known risks associated with the research interventions. The application for research should elaborate on the applicability of a DSMB for the proposed trial. To this end, research ethics committees and investigators should reference a decision in relation to guidelines proposed by Cairns and colleagues (5), which are adapted and summarized in the table below.

A DSMB is needed for a clinical trial whenever any one of the following are present
The trial has the power to detect statistically significant differences in tangible outcomes (mortality and significant morbidity).
When the risks asociated with the therapeutic components are not known. This is particularly applicable to pivotal phase 3 trials of investigational agents.
When the therapeutic components in either arm are known to be associated with severe adverse effects. This includes trials intended to evaluate approved agents for new medical indications.

When a DSMB is planned, certain information concerning its governance and monitoring plan should be provided in the application for research: the DSMB should be independent of the sponsor, and its members should not have any potentially disqualifying conflicts of interest in the outcome of the trial. Members with appropriate qualifications for defined roles should be chosen. The trial may be associated with more than one statistician, and they may be blinded or unblinded with respect to which outcomes are related to the arms of the trial. Guidance concerning this is available (6,7), and the choice for the proposed trial should be an informed one.

The application for research should list the name and affiliations for each DSMB member, and each should be associated with a declaratory statement concerning conflicts of interest, if any. The role fulfilled by each member should be stated.

The DSMB is responsible for periodic evaluation of the trial results, and may need to stop the trial for reasons of efficacy, safety or futility. Both significant positive and negative trends (8) necessitate careful evaluation. The DSMB has to balance the interests of the trial's participants against the need to acquire statistically valid results. The DSMB will evaluate interim results on a statistical basis (frequentist or bayesian), and should also consider the statistical evaluation in light of other information such as results of related trials, and an up−to−date Systematic Review pertinent to the trial (9).

Statistical techniques appropriate for trial monitoring have been described, and stopping guidelines for trial should be formulated in light of the nature of the trial, the nature of the interventions evaluated, and the nature of the adverse events and toxicity that may occur (10−11).

The application for research should specify the statistical techniques that will be used for interim results monitoring, and the stopping guidelines that will be used for the trial.

Communication of trial monitoring results and protocol changes to research ethics committees

In multicenter trials, information concerning interim results monitoring and protocol changes are typically transmitted to the principal investigator at each participating center. The investigator is responsible for providing this information to the committee, and ensuring that proposed protocol changes are reviewed and approved before they are instituted. Local research ethics committees recognize that this process of communication is unreliable and inefficient. Individual centers often become involved in the trial at different times relative to trial inception. Thus, this information should be made directly available −− on a continuing basis −− to local committees by the research sponsor. The availability of electronic communication and the Internet makes this feasible.

The feasibility and utility of using the Internet for the conduct of clinical trials has been established. Marks and colleagues (12) have described the web−based conduct of clinical trials wherein many trial−related functions are accomplished : site administration; center and subject recruitment; submission of data (electronic Case Report Forms) ; randomization; establishment of a "virtual" pharmacy for provision of drugs to participating centers; site monitoring; maintenance of security; and adverse event reporting. Many other items of information of interest to investigators, participants and the public may be provided. It would be technologically trivial for research ethics committees requirements to be included in this Web−based trial format. Involved committees could be notified by E−mail when new and pertinent information has been posted on the trial's Web site. The reader is referred to an example of this in the context of the INVEST (INternational VErapamil/trandolapril STudy) study for hypertension (13).

A multicenter clinical trial should be associated with a Web site wherein up−to−date trial−related information required by research ethics committees is provided. Committees should strongly encourage the conduct of Web−based clinical trials.

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