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(Friday 9:37am) 2 February 2001

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Ethics good practice policies and procedures (GPPP)

Definitions

beneficence, principle of *n* - A **principle** in **medical ethics** that asserts that the options available in treating or caring for one's fellow human beings is limited to that set which is justifiable on the basis of **beneficence**. Translated to research settings involving human beings, the principle means that only those acts, procedures, and **treatments** that meet this test are justifiable [Levine, 1986]. See also **medical ethics**, principles of.

clinical equipoise *n* - [due to Benjamin Freedman, 1987] In the context of **clinical trials**, a collective state of doubt or indecision as to choice or course of **treatment** due to absence of agreement among medical experts as to what that choice or course should be. rt: **frozen state of equipoise** ***Usage note***: The **randomized clinical trial** arises from a climate of clinical equipoise. Its ethical base rests on the presence of a collective state of doubt regarding the course of treatment, sufficiently balanced to justify **randomization**. In reality, a true state of equipoise is fleeting and fragile. Hence, a sustained state of equipoise over the course of a trial is, to a degree, a theoretical abstraction. Collective doubt waxes and wanes with the flow of data and expert opinion. The purpose of **treatment effects monitoring** is to determine whether data accumulating within a trial are sufficient to dissipate the state of doubt.

competence, principle of *n* - A **principle** in **medical ethics** that asserts that the care and **treatment** performed or offered in a **research** setting involving human beings must be offered in a **competent** fashion, consistent with accepted standards of care [Levine, 1986]. See also **medical ethics**, principles of.

demonstration trial *n* - 1. A **trial** that is undertaken to **demonstrate** the practicality or feasibility of administering some **treatment**; sometimes also **pilot trial** or **feasibility trial**. 2. A trial that is undertaken to establish or **prove** (defn 6) some treatment to be superior to another. rt: **community trial**, **effectiveness trial**, **field trial**, **management trial** ***Usage note***: Best avoided in the sense of defn 1; use **feasibility trial** or **pilot trial** to avoid confusion with uses in the sense of defn 2. Generally, use in the sense of defn 2 is in regard to a trial of an **effective** treatment aimed at **proving** its value so as to promote its use. **Demonstration** in the sense of defn 2 is likely to raise questions regarding the **ethics** underlying the trial to the extent that it is

motivated by a desire to **prove** the value of a treatment in the absence of a legitimate state of **equipoise**.

equipoise *n* - 1. A state of equilibrium or counterbalance; **equal ignorance**. 2. An individual or collective state of mind or belief characterized by a counterbalance of competing values, doubts, or **risks**. rt: **clinical equipoise** ***Usage note***: See **clinical equipoise** and **frozen state of equipoise**.

justice *n* - [ME, fr OF, fr L *justitia*, fr *justus*] The maintenance or administration of what is **just** and fair, especially by impartial methods and procedures. rt: **distributive justice**, **individual justice** ***Usage note***: An elusive concept. Often that which is seen as being **just** from one perspective is seen as being unjust from a different perspective. The issue of justice in **research** involving human beings (see usage note for **involve**) arises in regard to selection on both an individual and societal level, as discussed in the Belmont Report (so named because the conference leading to the report took place at the Belmont Conference Center of the Smithsonian Institute) of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burden and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (eg, adults before children) and that some classes of potential subjects (eg, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.* The report goes on to note that *Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual, and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.*

justice, principle of *n* - A **principle** in **medical ethics** that asserts that the care and **treatment** performed or offered in a research setting involving human beings (see usage note for **involve**) must be done in a **just** and **equitable** fashion, not to the **benefit** of a few or to the exclusion of others [Levine, 1986]. See also **medical ethics**, principles of. rt: **distributive justice**, **individual justice** ***Usage note***: See **justice**.

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medical ethics *n* - 1. A branch of **ethics** dealing with **medicine**; such a branch devoted primarily to a study of the ethics of **research** on human beings as performed in medical settings. 2. The **rules** and **standards** of conduct governing or guiding the medical profession.

medical ethics, principles of *n* - Standards set forth in the **Nuremberg Code** and subsequently enunciated in the form of principles having to do with the need for **beneficence**, **competence**, **justice**, and **respect** for persons when caring for **patients** and that serve as standards to be met in **clinical trials** or other forms of experimentation on human beings. See **beneficence**, principle of; **competence**, principle of; **justice**, principle of; **respect for persons**, principle of.

Mother test *n* - [**randomized trial**; jargon] The **test** of whether one would be willing to have one's Mother randomized to treatment in a trial; failure to meet the test may arise because of concerns regarding the treatment options offered, adequacy of the **consent form** or **consent process**, or because of an undesirable **risk-benefit ratio**.

nil treatment control *n* - 1. **null treatment control** 2. **trace treatment control**

null treatment control *n* - 1. A **control** (defn 1) not involving **treatment** of any form (including that represented by **placebos**). 2. **nontreatment control** rt: **nil treatment**

nontreatment control *n* - A **control** (defn 1) not involving use of any form of **treatment**; **observation control**.

respect for persons, principle of *n* - A **principle** in **medical ethics** that asserts that the care and **treatment** performed or offered in a research setting involving human beings must be done in a fashion denoting **respect** for those so involved [Levine, 1986]. See also **medical ethics**, principles of.

trace treatment control *n* - A **control treatment** involving a **trace treatment**.

P&P 1: In regard to randomized, parallel treatment trials, limit the choice of test and control treatments to that subset for which there is legitimate uncertainty as choice, ie, where states of clinical equipoise exist.

P&P 2: Cease randomization and treatment under a study protocol if data are sufficient to indicate the superiority or inferiority of a treatment.

P&P 3: Cease randomization and treatment under a study protocol if data external to the trial are sufficient to indicate the superiority or inferiority of a treatment.

P&P 4: Cease randomization and treatment under a study protocol if the ethical base for continuation has eroded or where continuation is unwise or ill-advised.

P&P 5: Do not participate in planning or conducting demonstration treatment trials.

Comment

One can argue they are unethical because they are done merely to demonstrate or "prove" what is already known.

P&P 6: Do not participate in planning or conducting trials not meeting the Mother Test.

P&P 7: Do not restrict or discourage access to care outside the confines of the trial.

P&P 8: Ensure that all persons, regardless of treatment assignment, receive care equalling or exceeding standard of care for the locale of conduct.

P&P 9: Limit use of nil or null treatment control treatments to settings in which treatment is not indicated and where nil or null treatment is consistent with prevailing norms and standards in the locale of conduct.

P&P 10: Placebo treatment should not be practiced if there is an accepted form of treatment.

P&P 11: The treatment procedures common to all persons enrolled into a trial should be regarded as part of the regimen of each treatment group and should be included as part of the discussion when the treatment groups are described to patients during the consent process.

P&P 12: Part of the training provided investigators before undertaking a trial should include the following:

- Review of the tenants of the Nüremberg Code and subsequent updates
- Review of the societal expectations of persons conducting research on human beings
- Review of research norms and standards
- Review of IRB requirements and procedures
- Review of integrity requirements and assurances practiced in research in general and in trials in particular
- Review of consequences of misconduct in science
- Review of safeguards and assurances for patients and procedures for protecting and ensuring same
- Review of procedures for reporting fraud or suspected misconduct
- Review of reporting procedures for adverse events
- Review of procedures for reporting and dealing with conflicts of interest
- Review of definition of insider trading (in the case of trials involving proprietary products of publicly traded companies)