7 January 1969

SUBJECT: Review of Department of the Army Policy on Use of Human Subjects in Research

1. PROBLEM. To review present Department of the Army (DA) policy on unclassified research projects involving use of human subjects to identify potential problem areas that DA should consider in further evolution of its policy.

2. ASSUMPTIONS.

a. The present climate of public opinion regarding the use of human subjects in research will continue for the foreseeable future.

b. Based on current reviews by the Public Health Service (PHS) regarding use of human subjects in medical investigations, it is assumed that PHS will publish a revised policy in the near future which will require a more formalized review of research applications submitted by civilian medical institutions to the PHS.

3. FACTS BEARING ON THE PROBLEM.

a. The present climate of public opinion regarding the use of human subjects for research reflects strong and serious concern for the rights of the individual in the experimental situation. This concern is based on the revelations of the Nuremberg Trials and the publicity given to the subject by Dr. Henry K. Beecher in his article in the New England Journal of Medicine of 16 June 1966. This climate has led in recent years to the Food and Drug Administration (FDA) regulation on "Informed Consent," the World Medical Association's, "Declaration of Helsinki," and the American Medical Association's "Ethical Guidelines for Clinical Investigation."

b. If the PHS policy is made more restrictive, this action will bring moral pressure on DA to review its procedures for the use of human subjects in medical investigations to insure that these procedures are consistent with the spirit of the revised PHS policy.

c. Current DA policy is outlined in the following three Army regulations:

(1) AR 70-25, Use of Volunteers as Subjects of Research, dated 26 Mar 62, see Annex A.

(2) AR 40-7, Clinical Use of Investigational Drugs, dated 21 Jul 67, see Annex B.

(3) AR 40-37, Radioisotope License Program (Human Use) dated 16 Aug 63, see Annex C.

d. Current requirements for review and approval authority for use of volunteers or patients for experimental investigations vary with the sponsorship of the project and other factors. A tabular summary of the current DA review and approval procedures, based on the AR's listed in para 3a is attached as Annex D. Depending upon the nature of the investigation the application may be reviewed by the Army Investigational Drug Review Board (AIDRB), the Preventive Medicine Division (PMD) of The Office of The Surgeon General (OTSG) and the Medical Research and Development Command (MRDC).

e. The Directorate of Professional Services (DPS), OTSG, may also review and approve use of investigational drugs in emergency treatment situations.

4. DISCUSSION.

a. Over the six years that have elapsed since publication of AR 70-25, DA policy on the use of volunteers has been commendable. A comparison of DA and PHS policies over this period reflects most favorably on DA because it formalized in AR 70-25, at an early stage following the 1961 amendments of the Food Drug and Cosmetic Act (FDCA), a policy of review of use of volunteers as subjects of research that was not paralleled by PHS in its grant program until 1966. This fact is perhaps a result of the extensive experience of DA with volunteer studies over the past 25 years and the serious consideration given over the entire period to the rights of the individual in such studies.

b. Present MRDC policy regarding review of research contracts and grants utilizing volunteers or patients as subjects of research varies considerably with the specialty area concerned. For research projects under review by the Armed Forces Epidemiological Board (AFEB) and its Commissions, intensive two-level review occurs with strong emphasis placed on ethical considerations. Furthermore, the AFEB review process makes a matter of record the details of such reviews. Although all MRDC contracts dealing with human subjects contain a special article outlining policy of The Surgeon General (TSG) regarding use of human volunteers, see Annex E, it appears that often no formalized review of record is made of contract applications in the non-AFEB area to insure that this policy is followed by the contractor.

c. Investigational drug studies represent a special area of activity of Army Medical Department (AMEDD). The AIDRB, under AR 40-7, has principal responsibility for this area. FDA does not routinely approve industry-sponsored drug studies prior to their initiation by industry, a fact that should be weighed by AIDRB in considering studies from that source. A legal

distinction should also be drawn in emergency treatment situations between therapeutic use of a marketed drug for an indication other than that for which the drug is labeled and use of a non-approved drug. These two situations place quite different levels of review responsibility on TSG and may for that reason probably require separate treatment by the AIDRB.

d. Drug studies with radioactive drugs are a special situation which is unique in that AR 70-25 and AR 40-37 specify that Secretary of the Army (SA) approval is required for any research with nuclear agents using volunteers. This restriction appears appropriate for studies of medical hazards of fallout materials or radiation from nuclear devices. However, the medical use of radioisotopes in patients for both diagnostic and therapeutic purposes is so common at this time that it appears logical to exempt it from specific approval by either SA or the Chief of Research and Development (CRD). This exemption is permitted under para 3c, AR 70-25. Similarly, the use of tagged investigational drugs is common in metabolic studies of investigational drugs sponsored by industry. The FDA policy is to consider tagged analogues of investigational drugs as comparable to the investigational drug itself. If DA were to follow this FDA policy, approval of the use of tagged investigational drugs in patients by the AIDRB and PMD, OTSG, should provide adequate review for such use. If such studies were performed in volunteers, approval by CRD would be appropriate. These procedures appear to be the intent of Memorandum for Record by LTC T. R. Ostrom, Subject: Approval for Requests for Use of Human Volunteers in Research, dated 1 Dec 65, see Annex F, and COL D. L. Howie's Memorandum for the Director of Army Research, Subject: AR 70-25, Use of Volunteers as Subjects of Research, dated 11 Jun 68, see Annex G. An earlier policy statement in a Disposition Form to TSG from CRD, Subject: AR 70-25, dated 25 May 64, see Annex H, appears to be at variance with later documents in para 3b in stating "It is the policy of this office to seek the approval of the Secretary of the Army for all research wherein human volunteer subjects are exposed to ionizing radiation from any type of source." Such a policy seems unnecessarily restrictive considering the wide-spread use of tagged investigational drugs in medical research today.

e. The use of investigational drugs in emergency treatment situations poses minor problems in identifying the group within OTSG responsible for approval of such uses. As noted in para 4c above, a legal distinction exists between marketed drugs used for new indications and non-marketed, non-approved drugs used for similar indications. In the first case, provided the drug is purchased in the marketplace and not provided by the manufacturer to the physician, the use of the drug by the physician for indications other than those for which the drug is labeled is considered within the realm of medical practice. The physician may embark on such uses on his own responsibility, guided by his professional knowledge and information available in the public domain concerning side effects, contraindications and adverse reactions. For such use of a drug approval by the DPS, OTSG, would be highly appropriate. For a drug not yet approved for marketing

emergency use is considered investigational use by the FDA, and under these conditions, approval of use by AIDRB would be consistent with the policy of requiring approval of other investigational drug studies by AIDRB.

f. The subject of investigational controls for studies of new medical devices in man is in a state of flux at this time. A recent court decision held that devices were subject to the FDCA (AMP Decision). An appeal of this decision was declined by the US Supreme Court. If the decision continues to be upheld by the courts, devices are subject to the same investigational controls as are drugs. FDA is not inclined to move rashly into this area, but may approach certain cases on a test case basis, e.g., intra-uterine devices. It is important for AMEDD to remain current in this area.

g. A review of AR's 70-25, 40-7 and 40-37 raises the question whether these three regulations could be integrated into a single regulation. This is an attractive possibility, particularly if such a combined regulation might be adopted as a DOD instruction.

5. CONCLUSIONS.

a. AR 70-25 is basically a sound approach to DA use of volunteers as subjects of research, fully in accord with PHS and FDA policy in the same area.

b. PHS policy changes concerning use of human subjects in research that are currently being discussed will, if implemented, place increased pressure on DA either to follow the pattern that PHS requires or to develop a different pattern better suited to DA. In either case, DA should insure that all use of human subjects, both volunteer and patient, in research be subjected to a medical-legal review to confirm that such investigations are conducted in accord with the highest ethical standards to protect the rights of the individual subject. There are three courses of action to consider as follows:

(1) The first approach would be to accept the new PHS policy and to require that all sponsoring institutions of contract and grant applications define their review process, create a review committee of appropriate membership, and periodically review all work conducted with human subjects in the institution. This approach would require the review of all AMEDD intramural research involving human subjects by an AMEDD or MRDC committee.

(2) The second approach would be not to accept the PHS approach but to review all research involving human subjects, whether extramural or intramural, by an AMEDD or MRDC committee.

(3) The third approach would be to move initially as outlined in para 5b(2) and to supplement this with the procedure of para 5b(1) within

a year or two after the new PHS requirements are accepted by the scientific and medical communities.

c. AR 40-7 should be reviewed for possible revision in the following areas:

(1) A clearer delineation of the respective responsibilities of MRDC, AIDRB, PMD and DPA in the review and approval of investigational drug studies.

(2) A decision whether the thrust of this regulation is "investigations" or "investigational drug studies."

(3) A delineation of the approval authority for investigational studies of marketed vs. non-approved drugs.

(4) A reevaluation of the approval requirements of Phase I and II vs. Phase III drug studies, considering that FDA does not approve such studies before they are initiated and that the former involve significantly greater hazard than the latter.

d. AMEDD should be aware of recent legal decisions supporting the position that medical devices fall under the provisions of the FDCA. Consideration should be given, as policy evolves in this area, to reviewing research investigations involving human subjects and new devices under guidelines similar to those now employed with drugs. The position can also be taken that, irrespective of the legal question, all research studies using human subjects, whether involving drugs or devices, should meet the same criteria of ethical propriety.

e. Consideration should be given at a later date to consolidation of AR's 70-25, 40-7, and 40-37 and to proposing such a consolidated regulation for DOD issuance.

f. Consideration should be given to formally revising CRD policy regarding approval authority for use of radioisotopes as follows:

(1) That all studies in volunteers of hazards of by products or radiation of military nuclear devices or energy sources be referred to the Secretary of the Army for approval.

(2) That all other studies involving use of radioisotopes in volunteers be referred to CRD for approval.

(3) That all other studies involving use of radioisotopes in patients be referred to TSG for approval.

6. ACTION RECOMMENDED.

a. That the DF attached as Annex I be signed to transmit this study to AMEDD for information and comment, particularly in regard to the choice of options listed in para 5b.

b. That following receipt of comments from AMEDD, this report and their comments be reviewed to prepare a position paper recommending change of DA policy regarding approval of radioisotope studies in man as outlined in para 4d.

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