ARM1.940713.040 Incl 1

MEMORANDUM FOR RECORD October 18, 1974

THE REVIEW PROCESS FOR RESEARCH INVOLVING HUMAN SUBJECTS IN THE US ARMY AND A PROPOSAL FOR CHANGE

(This memorandum examines the review mechanisms for research involving human subjects in the Army in the light of currently changing federal policy. The present administrative framework regulates Army teaching hospital research very closely but does not adequately review other activities. Adoption of relatively simple changes at the Office of The Surgeon General level will result in a more efficient and uniform system of Human Use Review in the Army.)

I PRESENT REVIEW PROCESSES

A. Medical Department Hospitals.

Research involving human subjects in Army teaching hospitals is regulated by a local Clinical Investigation Committee and a Human Use Committee accord- to the provisions of AR 40-38. The purpose and composition of each local committee is specified as follows in that AR:

> Clinical Investigation Committee--"To review all clinical investigation proposals for scientific aqequacy and to set priorities for support. This committee will be composed of the Chief, Professional Service or his designated representative who will act as Chairman, and at least six other medically qualified individuals designated by the hospital commander."
>
> Human Use Committee--"To review for medical safety and suitability all clinical investigation protocols involving the use of human subjects. This committee will be composed of the Chief, Professional Services, who will act as Chairman, a Chaplain, a JAG officer and four other qualified individuals designated by the Commander of the hospital, who are not members of the Clinical Investigation Committee."

Hospitals which do not have established local committees (i.e. most non-teaching hospitals) must submit protocols directly to the Surgeon General after they have been approved by the local hospital commander.

After research proposals have been approved by both local committees and by the teaching hospital commander, virtually all are submitted for TSG approval prior to the initiation of the study. AR 40-38 states in paragraph 4(g) that:

> "Proposals in the following categories must be approved by The Surgeon General prior to initiation of investigation:
> (1) When funding requirements exceed $5,000.
> (2) When human subjects are used.
> (3) When investigational drugs are employed in humans, or any

use is made of Schedule I controlled substances. See AR 40-7.
(4) When radioisotopes are used. See AR 40-37.
(5) When a proposal is concerned with drug or alcohol abuse."

(In practice, not all protocols involving human subjects have received TSG approval since some committees have interpreted the word "subject", defined in paragraph 3c of AR 40-38 as "any person who may be at risk because of participation as an object of Clinical investigation," to mean only those persons who are at a definite risk of being physically harmed by the study procedures. Thus, some local committees have tried to make the distinction between "at risk" and "not at risk" studies so that only the "at risk" type study plans are sent for prior TSG approval.)

Protocols using human subjects which are sent for approval by TSG are considered by a TSG Clinical Investigation Committee(CIC) and Human Use Committee(HUC). The composition of these bodies closely parallels that of the local committees. The CIC is composed entirely of MC officers and the Human Use Committee includes a Chaplain, a JAG officer and several other "non-medical" persons in addition to the Chairman who is an MC officer. The decisions of these committees must be approved by TSG before final approval is granted.

If the proposal involves an investigational drug, the AIDRB must consider it. The composition of the AIDRB is nearly identical to the CIC. A JAG officer sits as a non-voting member of the AIDRB as well as on the HUC but not on the CIC. An OTSG Memorandum in press entitled "Human Use Review Office" awknowledges the nearly identical expertise of the CIC and AIDRB and states that proposals approved by the AIDRB need not be considered by CIC unless funding approval is needed.

Figure 1 is a schematic of the teaching hospital proposal review process. It includes approval by two local committees, as many as three TSG committees, the local commander and TSG. The committees all meet separately and generate separate sets of minutes. At OTSG level, the process requires TSG signature for approval of the same protocol on two or three separate occasions.

B. US Army Medical Research and Development Command Laboratories.

In contrast to the complex procedure for Army hospitals, the present review process for proposals from in-house laboratories is simple. Proposals are reviewed by laboratory commanders and by his committee of scientific advisors. In accordance with AR 70-25, September 1974, proposals are then submitted for approval to TSG. Although the proposals receive thorough professional review, no formal Human Use Committee action is required. Protocols involving investigational drugs must also be considered by AIDRB.

C. USAMRDC Contractors and Grantees.

All contract proposals are reviewed in detail by the Contract Review Board if they involve the use of human subjects. The Board includes a JAG officer and medical professional people in addition to contracting officers and comptroller representatives. The professional members, with one exception, are on either the OTSG CIC or the AIDRB or both. The Command requires that contractors provide local institutional Human Use Review which generally fulfills the requirements set forth by the Department of Health, Education and Welfare. Protocols involving investigational drugs must also be considered by the AIDRB.

D. Other Department of The Army Research Involving Human Subjects.

Other Army units are required by AR 70-25 to submit protocols to TSG for review if they involve the use of human subjects. Usually, local committee review is unavailable and TSG review is performed as for an in-house project.

II DHEW REGULATIONS PERTAINING TO THE REVIEW OF RESEARCH INVOLVING HUMAN SUBJECTS.

A. Regulations which have been adopted.

The new DHEW regulations, effective 1 July 1974 are in Title 46, Code of Federal Regulations, Subtitle A, Part 46 (Federal Register Vol 39, 18917). The review mechanism required by these regulations for DHEW contractors and grantees consists of a single local institutional human use review committee. Contractors and grantees are required to submit assurances of proper local review of activities involving human subjects to DHEW in order to receive funds. Prior DHEW review of final plans or experiments is not required. A system for DHEW review of detailed plans was proposed but rejected in the final rulemaking because it was concluded that the requirement was "impractical and unrealistic." (Fed Reg 39, 18916)

The required characteristics of the local institutional review committee are as follows:

46.6 (b) (1) "The committee must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the organization. The Committee must be sufficiently qualified through the maturity, experience, and expertise of its members and the diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the committee must be able to ascertain the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice and community attitudes. The committee must therefore include persons whose concerns are in these areas.

(2)The committee members shall be identified to DHEW by name; earned degrees, if any; position or occupation; representative capacity; and by other pertinent indications of experience such as board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to the committee deliberations. Any employment or other relationship between each member and the organization shall be identified, i.e. full-time employee, member of governing panel or board, paid consultant, unpaid consultant. Changes in committee membership shall be reported to DHEW in such form and at such times as the Secretary may require.
(3) No member of a committee shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the committee.
(4) No committee shall consist entirely of persons who are officers, employees, or agents, of, or are otherwise associated with the organization, apart from their membership on the committee.
(5) No committee shall consist entirely of members of a single professional group.
(6) The quorum of the committee shall be defined, but may in no event be less than a majority of the total membership duly convened to carry out the committee's responsibilities under the terms of the assurance."

B. Proposed DHEW Rules Pertaining to Research Involving Minors, Fetuses, Abortuses, Prisoners and the Institutionalized Mentally Disabled. (Federal Register 39, 30648, August 23, 1974)

The proposed rules deal with groups of subjects who are felt to need special protection because of questions about their ability to provide informed consent for experimental procedures. The proposed rules do not deal with children as test subjects. The statement of proposed policy awknowledges the establishment of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research by Public Law 93-348. The Commission has the charter to:

"(i) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, (ii) develop guidelines which should be followed in such research to assure that it is conducted in accordance with such principles, and (iii) make recommendations to the Secretary (I) for such administrative action as may be appropriate to apply such guidelines to biomedical and behavioral research donducted or supported under programs administered by the Secretary, and (II) concerning any other matter pertaining to the protection of human subjects of biomedical and behavioral research."

These proposed rules are intended to be part of a "continuing dialogue"

about what policy and administrative framework is needed to protect human subjects. It is likely that final rules will follow guidelines recommended by the Commission after its two year term is completed.

The proposed rules would require two new committees to be established to review work involving these special groups of subjects. They are: 1) An Ethical Advisory Board to review activities involving Fetuses, Abortuses, pregnant women and in vitro fertilization,

and 2) local institutional "consent committees" to supervise activities invoving fetuses, abortuses, pregnant women, invitro fertilization, prisoners, and institutionalized mentally disabled people as subjects. The sections describing these proposed committees are included below.

46.304 Ethical Advisory Board.

"(a) All applications or proposals for the support of activities covered by this subpart shall be reviewed by an Ethical Advisory Board, established by the Secretary within the National Institutes of Health, which shall advise the funding agency concerning the acceptability of such activities from an ethical standpoint.

(b) Members of the Board shall be so selected that the Board will be competent to deal with medical, legal, social, and ethical issues and shall include, for example, research scientists, physicians, lawyers, and clergy and/or ethicists, as well as representatives of the general public. No Board member may be a regular full-time employee of the Federal Government.

46.305 Establishment of a consent committee.

"(a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided an assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the Secretary) for each such activity, to oversee the actual process by which individual consents required by this subpart are secured, to monitor the progress of the activity and intervene as necessary, and to carry out such other duties as the Secretary (with the advice of the Ethical Advisory Board) may prescribe. The duties of the consent committee may include:

(1) Participation in the actual selection process and securing of consents to assure that all elements of a legally effective informed consent, as outlined in Section 46.3, are satisfied. Depending on what may be prescribed in the application or offer approved by the Secretary, this might require approval by the committee of individual participation in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.

(2) Monitoring the progress of the activity. Depending on what may be prescribed in the application or offer approved by the Secretary, this might include: visits to the activity site, identification of one or more committee members who would be available for consultation with those involved in the consent procedure (i.e., participants) at the participant's request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the participants, periodic contact with the participants to ascertain whether they remain willing to continue in the activity, providing for the withdrawal of any participants who wish to do so, and authority to terminate participation of one or more participants with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of the members designated as chairperson.

(c) Where a particular activity, involving fetuses in utero or pregnant women, presents negligible risk to the fetus, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may (with the advice of the Ethical Advisory Board) grant the request in while or in part.

(d) The requirements of this section and Section 46.304 do not obviate the need for review and approval of the application or offer by the organizational review committee to the extent required under Subpart A of this part."

III CRITIQUE OF THE ARMY ADMINISTRATIVE FRAMEWORK FOR REVIEWING RESEARCH ON HUMAN SUBJECTS IN RELATIONSHIP TO PRESENT AND FUTURE FEDERAL POLICY

A. Local Institutional review.

The DHEW system of review places heavy emphasis on local institutional review committees. Recent changes and proposed rules continue to make these committees the backbone of the review process.

The Army teaching hospital CIC and HUC adequately fill this role and could readily be adapted to proposed changes such as the formation of "consent committees." The dual, independent committee system at the local level exceeds DHEW requirements. The present Human Use Committees fail to meet minimal requirements only in that they are usually composed entirely of Army personnel. The new rules would require that the committees have some members who are not DA or DOD employees.

USAMRDC contractors generally have access to DHEW approved institutional review committees. In house laboratories do not presently have Human Use Committees. A USAMRDC Regulation in preparation will establish the requirement for such committees and will also specify prodedures for certification of contractors' committees in accordance with DHEW policy.

B. Surgeon General Review of Research Involving Human Subjects.

AR 70-25, September 1974, added responsibility for prior review of non-hospital activities involving human subjects to TSG'S previously held responsibility for hospital research. Except for the proposed requirement for an Ethical Advisory Board at NIH to review a limited number of protocols, DHEW is unlikely to require this sort of central control of the activities which they fund. This administrative arrangement is highly advantagous to the Army since it provides additional protection for human subjects and allows uniform standards to be applied to all Army research. A potential disavantage is that research progress may be impeded by unnecessary beaurocratic machinery.

The present OTSG system of review for hospital proposals is an inefficient process. AR 40-38 has set up a dual committee system at OTSG level which parallels the system for local review. There is no requirement for such a complex system in any present or proposed federal policy. Although separate deliberations by the HUC and CIC are important to the independent review process at the hospital level, this is unnecessary for review at TSG level. The present arrangement results in unavoidable delays as well as confusion as each TSG committee reviews the same protocols without the benefit of guidance from the others.

The OTSG review process for contract and in-house proposals is administratively simple but is not optimal since no properly constituted Human Use Committee has the responsibility for providing recommendations to TSG.

MFR: REVIEW PROCESS FOR RESEARCH INVOLVING HUMAN SUBJECTS IN THE ARMY

There is a need for a revised procedure for reviewing research involving human subjects by TSG. The objectives of this revision should be:

1) Reorganization of working committees reviewing hospital research to provide thorough, efficient and hopefully rapid action.
2) Provision of the same type of review for all types of Army research with humans in-house laboratories, hospital clinical investigation programs and contractors.
3) Provision of a non-DOD Ethical Advisory Board to provide independent review of the overall Army use of human subjects and to provide specific recommendations on proposals involving special groups of subjects (e.g. prisoners, fetuses) as directed by TSG.

IV PROPOSAL FOR A COMBINED HUMAN USE REVIEW COMMITTEE AND ETHICAL ADVISORY BOARD TO REVIEW HUMAN USE FOR THE SURGEON GENERAL.

A. Combined Human Use Review Committee(CHURC).

As directed by TSG, the CHURC would review research proposals requiring TSG approval under existing Army Regulations. The Committee would possess the expertise to judge the scientific merit of protocols, including investigational drug protocols, and to determine their acceptability in terms of current TSG and national policy on ethical research. The committee would be composed of the combined membership of the AIDRB and CIC in addition to five members chosen on the basis of their ability to evaluate ethical and legal issues. At least one lawyer and one clergyman should be on the committee. At least two of the members should not be employees of the Department of the Army.

The AIDRB and CIC would maintain their respective committee structures under existing AR's for the purpose of conducting business which does not require approval by the full committee. Meetings of the CHURC will be conducted by a Chairman who will be the Assistant Surgeon General for Research and Development or his designee. The Chairman will see that quorum requirements for action by the CIC and/or AIDRB are met when the combined committee meets. Committee decisions will be recorded to show that all necessary action for a recommendation to TSG has been taken at the same meeting. For example, action on an investigational drug protocol might be recorded as: " The Combined Human Use Review Committee, meeting as the AIDRB, approved the proposal..." The committee minutes will be submitted to TSG for Approval. The Human Use Review Office will process protocols for the committee in accordance with pertinent directives.

B. Ethical Advisory Board.

Much of the work involving human subjects in the Army is obviously ethical and non-controversial. For this large proportion of the Army research with humans, review by internal TSG committees is adequate and in keeping with the highest standards of review anywhere in the world. A certain portion of the work, however, involves substantive ethical and/or political-social issues. In order to provide credible review of this work, it is proposed that an independent advisory board be established along the lines of the proposed DHEW Ethical Advisory Board. This group would be

composed of well-known and respected people who are not employees of the Department of Defense or its agencies. This group would be tasked to review specific test plans from time to time as requested by TSG and to advise TSG about the operation of the Human Use Review System and about new requiremens of changing policy in this area. It is proposed that the National Academy of Sciences be asked to set up and operate this committee.

C. *Impact of the Proposed Changes on OTSG and USAMRDC Functions.*

1) The mebership on the AIDRB and Clinical Investigation Committees is quite similar. Thus, combinig the two committees for purposes of reviewing activities involving human subjects will not increase the size of the Combined Committee excessively. Vis:

CIC Membership	AIDRB Membership
-a) ASG/R&D or Designee, Chairman	-a) ASG/R&D or Designee, Chairman
-b) Med Consult, Dir, HCO	-b) Med Consult, Dir, HCO
-c) C, Health and Env, Dir, HCO	-c) C, Health and Env, Dir, HCO
-d) Surg Consult, Dir. HCO	-d) Surg Consult, Dir. HCO
-e) Dir Med Res, USAMRDC	-e) Dir Med Res, USAMRDC
f) Dir Surg Res, USAMRDC	f) Pharmacy Consultant, Dir. HCO
g) Lab Sci Consult, Dir. HCO	

When the chairmen of the two committees are different (i.e. different designees), the total membership of the Combined Committee will be fourteen(14) including the five members whose expertise is in the area of ethical-legal issues.

2) The present separate TSG Human Use Committee structure will be absorbed into the Combined Committee. That committee will no longer have a separate identity aside from the Combined group. Members of the present committee might be eligible to serve on the new group.

3) The Combined Committee will allow efficient coordination between the Directorate of Health Care Operations and the USAMRDC on all proposals so that a coordinated recommendation can be made to TSG. This benefit will become much more important when the Directorate of Health Care Operations moves to the Pentagon.

4) Responsibility for review of human use aspects of USAMRDC contract work could be delegated to the CHURC because of its broad membership which includes adequate representation from the R&D Command. This would allow the Contract Review Board to limit its meetings to financial considerations.

5) The proposed arrangement will make thorough, efficient review easier by allowing the "ethical-legal" type members to deliberate with the more scientifically oriented members. Most members of the present committees would agree that separating the two groups is artificial when questions of "risk vs. benefit" are being considered.

5) The new arrangement will save resources because duplicate and triplicate preparation and TSG approval of minutes involving the same protocols will be avoided.

6) The new arrangement will require no immediate changes in Army Regulations since there is no stipulation now that requires that established OTSG committees meet separately.

3) A schematic diagram of the proposed review process is shown in Figure 2.

Michael V. Johnston, M.D.
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ATTACHED: Figures 1 & 2.

Figure 1. Approval Process for Research Proposals Using Human Subjects in Army Teaching Hospitals.

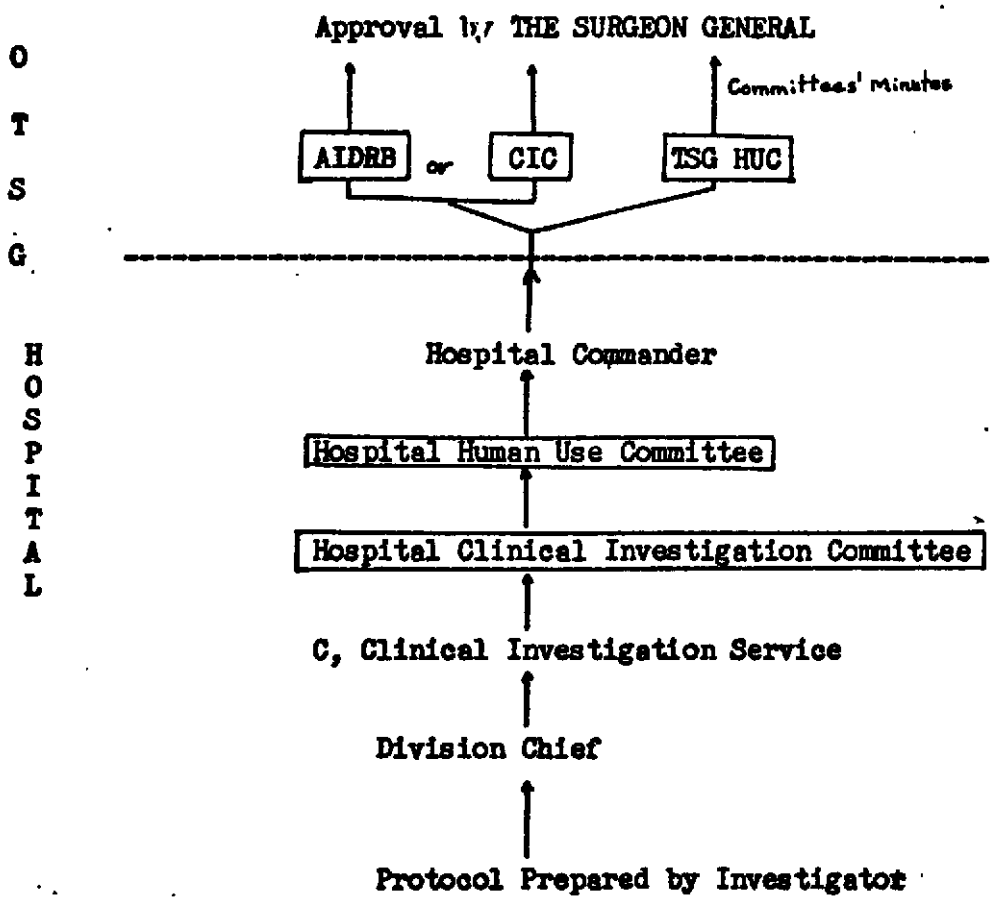
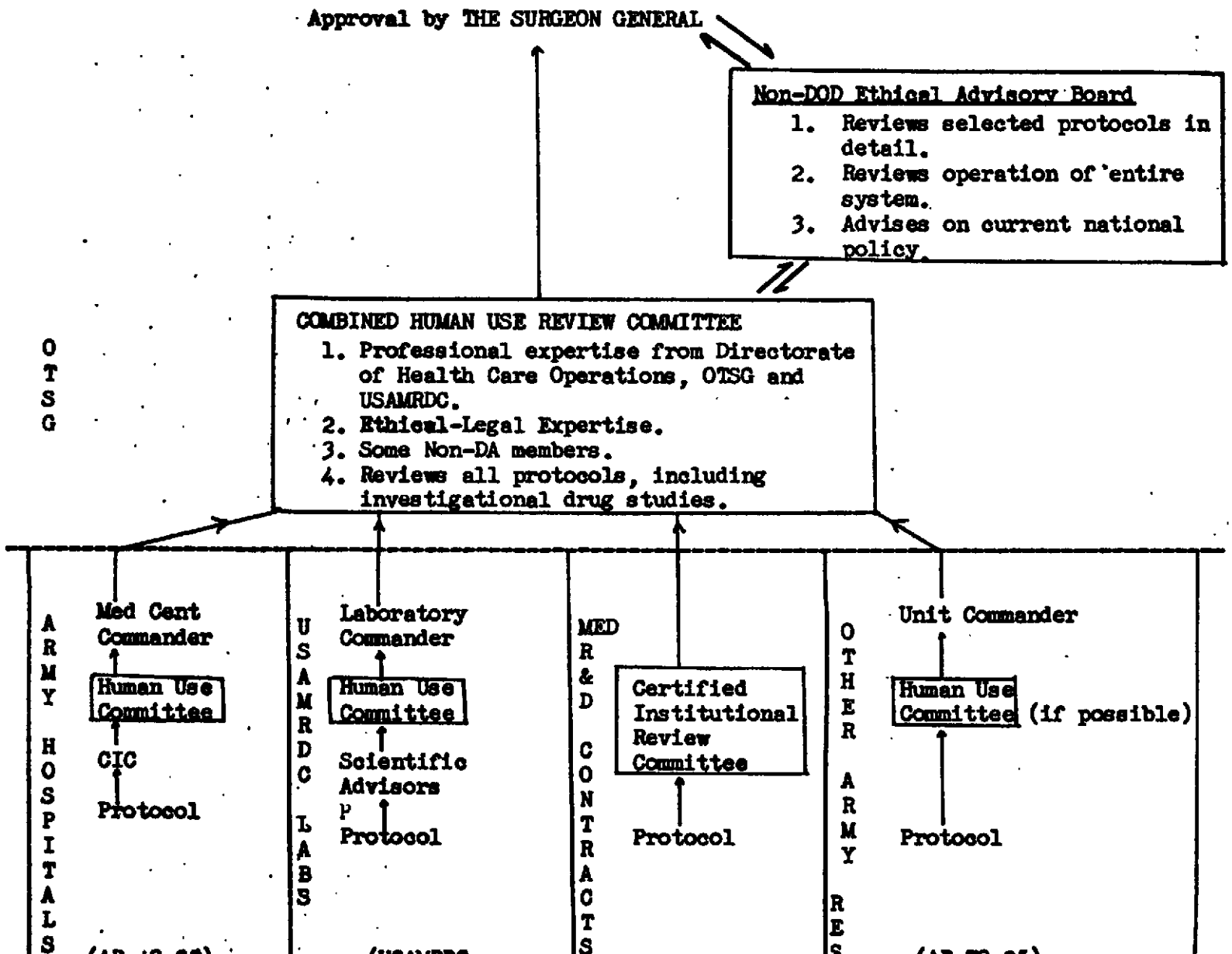
Figure 2. Proposed Review Process for Army Research Involving Human Subjects.