Lactic acidosis often has a subtle onset and nonspecific symptomatology which may include malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The investigator as well as the patient must be aware of the possible importance of such symptoms and the patient should be instructed to notify the investigator immediately at the onset of any such symptomatology. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. For metformin blood level measurements, venous blood should be drawn into a 7 ml heparinized Vacutainer®. After thorough mixing by inversion, a 2 ml aliquot of whole blood should be transferred to a polypropylene transfer tube. The remaining whole blood should be centrifuged (2500 rpm for 15 min. at 5°C) with subsequent transfer of supernatant plasma to a second polypropylene transfer tube. Both samples should be stored promptly in a freezer at -20°C, until sent to a location indicated by the sponsor. (Serial samples may also be helpful.)

Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious etiologies.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency which must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to both correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of

symptomatology and recovery.

NOTE: CORNING PACT MUST BE INFORMED IMMEDIATELY BY TELEPHONE OF SUCH AN EVENT AT 1-800-321-2330

IX. SAFETY REPORTING

A. Reporting Safety Information

Timely and complete reporting of serious adverse events occurring in association with test drug administration aids the sponsor in identifying reactions that are potentially drug-related, thereby allowing: a) a greater understanding of drug effects; b) recognition of dose-related drug effects; c) appropriate modification of study protocols; and d) adherence to regulatory requirements that are designed to protect the patient, prescribing physicians, and sponsor.

Patient experiencing serious adverse events that result in treatment discontinuation or that are ongoing at the end of their participation in the study should have appropriate follow-up until such time as the event resolves, the patient's condition stabilizes, or until it is determined that the event is not due to the study drug. The serious adverse event should be recorded on the TERMINATION PAGE of the CRF. Any relevant follow-up information regarding **serious** adverse events should also be reported on supplemental SERIOUS ADVERSE EVENT REPORT pages of the CRF.

If pregnancy occurs during the course of this study, the monitor at Corning PACT must be notified immediately via telephone or confirmed facsimile (FAX), and this information must also be recorded on the SERIOUS ADVERSE EVENT page of the CRF. Outcome of the pregnancy and status of the newborn must also be reported. Neonates must be followed up for ≥ 8 weeks.

B. Serious Adverse Events

A serious adverse event is one which meets any one of the following criteria:

a. Fatal or Life-threatening
b. Permanently or substantially disabling
c. Requiring or prolonging inpatient hospitalization
d. A congenital anomaly
e. Cancer
f. Overdose

When a serious adverse event occurs, the investigator must also immediately send a completed SERIOUS ADVERSE EVENT REPORT (supplies of these forms may be found in the Study Notebook) and telephone the contact person listed below within 24 hours of learning of the event.

Primary Contact:

Corning PACT
One Radnor Corporate Center
Suite 300
Radnor, PA 19087
1-800-321-2330

Secondary Contact:

Sandra Raff, M.D.
Director, Clinical Trials, Metabolism
Bristol-Myers Squibb
(609) 897-2878
(609) 897-6439 FAX

These REPORTS must be completed whenever a serious event occurs, regardless of its causal relationship to test drug therapy. If only limited information is initially available, follow-up reports will be required.

All serious adverse event information reported to Corning PACT will be relayed to Bristol-Myers Squibb.

During the course of the study, and in accordance with U.S. Federal regulations, Bristol-Myers Squibb will notify investigators by letter of newly apparent, serious adverse events not previously described in the Investigator's Brochure or package insert. It is the responsibility of the

Investigator to notify the governing IRB of these events.

C. **Follow-up of Reports of Hospitalization and Death**

Hospital records and death certificates will be requested and reviewed. To ensure that lactic acidosis cases and deaths are identified, each hospitalization, death and drug cessation will be carefully characterized. Information will be obtained from the investigator, other health care providers involved in the cases, and hospital and death records. If initial data review indicates an admission for a metabolic reason, the discharge summary, death certificate, electrolyte and blood gas data, when available, will be obtained. These will then be characterized as ketoacidosis, possible lactic acidosis (anion gap present), and acidosis not-otherwise-specified and other.

Preliminary causality assessment will be performed by the investigator and reviewed by the sponsor and/or sponsor-designated safety committee. The sponsor will submit assessment reports in accordance with applicable regulations.

X. STATISTICAL CONSIDERATIONS

A. **Overview**

All patients enrolled into the study will be accounted for. All enrolled patients who have been prescribed study medication will be analyzed for safety.

A major outcome variable to be evaluated is the incidence of clinical lactic acidosis among the patients who receive metformin (as monotherapy or as combined therapy) vs those receiving usual care. Reports from international sources (see above, II. INTRODUCTION) indicate that the reported incidence of lactic acidosis among patients treated with metformin is of the order of 3 per 100,000. Events of this extremely rare frequency cannot be detected in clinical trials. However, with the sample size of 8,000 patients, rare adverse events, occurring with a frequency of 5 per 10,000 or higher can be identified.

The primary analysis will include the estimation/comparison of incidence rates in the metformin exposed patients to those not exposed to metformin (the internal comparison group receiving usual care), for the following: 1) hospitalization for lactic acidosis; 2) hospitalization for metabolic cause; 3) all cause hospitalizations; 4) death due to lactic acidosis; 5) all cause death; 6) severe hypoglycemia requiring medical intervention: and 7) all serious adverse events . Each hospital admission will be counted as a separate event.

In addition, estimates of the expected rates of hospitalizations, hospitalizations for metabolic cause, and deaths in patients with NIDDM may be made using external comparators, if appropriate existent data bases can be identified. These will be refined in accordance with the actual age, gender and disease profile found after enrollment is complete. A supplementary outcome analysis may then consist of observed vs. expected ratios for these critical events.

B. **Sample Size Determination**

The sample size of 8000 metformin patients will be sufficiently large to provide 95% assurance to detect events occurring at a rate of 5 per 10,000 or higher. For Phase IV studies intending to examine relatively uncommon safety effects, confidence interval considerations usually have been recommended [18]. Thus, a confidence interval approach will be used to demonstrate that the incidence of lactic acidosis is lower than a small number, e.g., 5 per 10,000. The calculations of confidence interval for incidence rates are presented below.

# of Cases Observed in 8000 Metformin Patients	Rate in Metformin Patients	Approximate 95% Confidence Intervals
0	0	(0 - 0.00024)
2	0.00025	(0 - 0.00060)
5	0.000625	(0.00007 - 0.00118)
10	0.00125	(0.00046 - 0.00204)
	0.0025	(0.00138 - 0.00361)

50	0.00625	(0.00449 - 0.00801)

The sample size of 8,000 and 2,000 patients, respectively, in the metformin and usual care arms will also provide approximately 80% power in detecting a two-fold risk difference between the treatment groups for a background event rate of 5 per 1000. The selected sample size will provide 80% power to detect the following differences in incidence rates:

Incidence Rate in Control Group	Incidence Rate in Metformin Group	Relative Risk
0.0005	0.00405	8.10
0.001	0.0051	5.10
0.005	0.0116	2.32
0.01	0.01855	1.86

For lactate determination a sample size of 456 metformin and 114 usual care patients will provide 80% power in detecting a 0.5 mmol/L difference in plasma lactate levels.

C. Statistical Methods

Baseline comparability among treatment groups and demographic information and other patient characteristics at baseline will be assessed.

The incidence rates of serious adverse events will be compared using Fisher's exact test or Chi-square test for treatment group differences. The percentage of patients experiencing specified serious adverse events or hospitalization for lactic acidosis will be compared among treatment groups by Fisher's exact test or Cochran-Mantel-Haenszel test, stratifying for study center.

The frequency of and reasons for discontinuation will be described.

Other analyses will be performed as deemed appropriate by sponsor,

investigator, and statistician.

XI. INSTITUTIONAL REVIEW BOARD APPROVAL

Before enrollment can begin, the investigator must provide the sponsor with written evidence that the protocol and written informed consent document have been reviewed and approved by an appropriately constituted Institutional Review Board (IRB). Any advertisement used for recruiting prospective study candidates must be reviewed and approved by the IRB. The IRB must consist of at least five (5) members of varied backgrounds (including persons other than scientists). (See Appendix B).

XII. CASE REPORT FORM COMPLETION

A case report form, designed by the sponsor will be provided for each patient. Please note the following:

1. All forms must be filled out using black ball point pen or typed.

2. All information requested on each case report form page must be provided. In circumstances when information is not available or unobtainable, an NA (not available) or ND (not done) should be entered.

3. Correction(s) of data on the case report form can only be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

4. If any changes are made to a case record form after it has been signed and dated by the investigator (e.g. corrections or new data entered in an area previously blank), the entry must be initialed and dated by the individual making the entry. If that individual is not an investigator, an investigator must initial and date the Investigator Statement, or each page that was changed, to indicate awareness and agreement with the change.

5. Do not record any data on back of any case report form pages.

6. If requested, the results of laboratory tests required by this protocol should be affixed to the appropriate page of the case report form.

7. The investigator must sign and date the Investigator Statement on the final page of the case report form. The investigator's statement will read as follows:

I certify that I have carefully examined and verified all entries on this case record form. All information entered onto these forms by myself and/or my associate is correct.

Federal law requires that all case record forms and all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing record, etc.) which support case report forms of this study, must be retained in the files of the responsible investigator for a period of 2 years following the date a marketing application is approved for the indication for which the drug is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the entire investigation (not merely the investigator's portion) is officially discontinued and, for IND studies, the FDA is notified. If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody may be transferred to a person who accepts the responsibility. Bristol-Myers Squibb must be notified in writing of the name and address of the new custodian.

XIII. MONITORING/AUDITING ACTIVITIES

A. Monitoring Requirements

Contact with investigator will be maintained by appropriate representatives of Corning PACT and Bristol-Myers Squibb who will visit a randomly selected 10% sample of investigative sites at periodic intervals for the purpose of discussing or retrieving data.

At the time of the monitoring visit, the investigator will have available the following documents: complete case report forms, patient records (i.e., office or hospital charts, laboratory reports and consent forms) and the Study Notebook.

B. **Audit Procedures**

The United States Food and Drug Administration, in the person of a trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying.

Similar auditing procedures may also be conducted by a representative of Corning PACT and Bristol-Myers Squibb Regulatory Compliance Department. The investigator agrees to cooperate with the auditor during his visit and will be available to supply the auditor with case report forms or other files necessary to conduct the audit. Any findings will be strictly confidential.

C. **Study Directory**

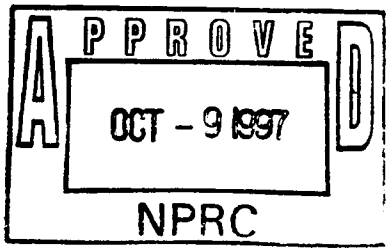
1. Bristol-Myers Squibb:

Sandra Raff, M.D.
Director, Clinical Trials, Metabolism
Bristol-Myers Squibb
(609) 897-2878
(609) 897-6439 FAX

Donna Mills, RN BSN
Associate Director, Clinical Trials, Metabolism
(609) 897-2764
(609) 897-6439 FAX

2. Corning PACT:

James Peterson, MAS
Manager Medical Research Group
Corning PACT
One Radnor Corporate Center
Suite 300
Radnor, PA 19087
1-800-321-2330



XIV. **INVESTIGATOR AGREEMENT**

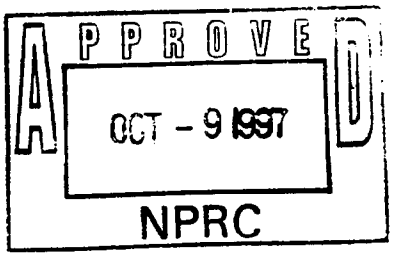
Except for an emergency situation in which proper care for the protection, safety and well being of the patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be documented and explained to Bristol-Myers Squibb and the IRB.

Should a revision or addendum to the protocol be required it will be prepared and approved by Bristol-Myers Squibb.

By signing below the investigator agrees to perform the protocol CV138-002 Addendum A entitled "Comparative Outcomes Study of Metformin Intervention versus Conventional Approach: The COSMIC Approach Study" as described in this document.

Investigator Signature _____ Date _____

Investigator's Printed Name _____



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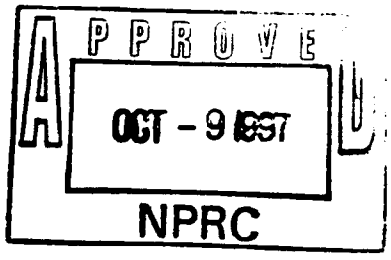

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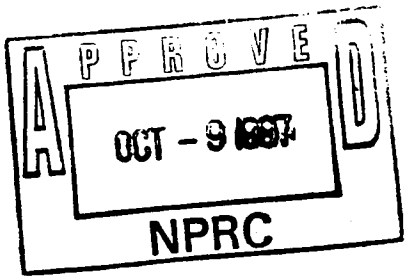


APPENDIX A

CONSENT FOR USE OF INVESTIGATIONAL DRUGS ON HUMAN SUBJECTS: STATEMENT OF POLICY

The investigator is required to insure the sponsor that informed consent of human subjects has been obtained in accordance with Rules and Regulations Part 50 (Informed Consent of Human Subjects), 21 CFR Ch. 1 (4-1-92 Edition).

SUBPART B - INFORMED CONSENT OF HUMAN SUBJECTS:

50.20 GENERAL REQUIREMENTS FOR INFORMED CONSENT

Except as provided in 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

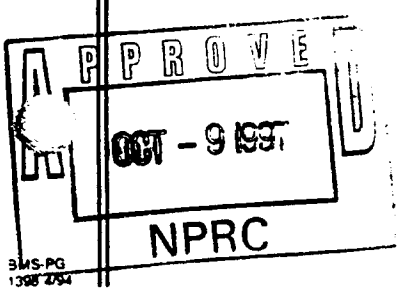
50.25 ELEMENTS OF INFORMED CONSENT

a. Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2) A description of any reasonably foreseeable risks or discomforts to the subject.

3) A description of any benefits to the subject or to others which may reasonably be expected from the research.



4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information maybe obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

b. Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

2) Anticipate circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

3) Any additional costs to the subject that may result from participation in the research.

4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the study subject.

6) The approximate number of subjects involved in the study.

c. The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

d. Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

50.27 DOCUMENTATION OF INFORMED CONSENT

a. Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

b. Except as provided in 56.109(c), the consent form may be either of the following:

1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

2) A "short form" written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or to the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or to the representative in addition to the copy of the short form.

APPENDIX B

ORGANIZATION AND PROCEDURAL REQUIREMENTS INSTITUTIONAL REVIEW BOARDS: STATEMENT OF POLICY

Clinical investigations must be subject to prior and continuing review and approval by an independent institutional review board in accordance with Title 21 of the Code of Federal Regulations, Part 56 (Institutional Review Boards), 21 CFR Ch. 1 (4-1-92 Edition).

SUBPART B - ORGANIZATION AND PERSONNEL:

56.107 IRB MEMBERSHIP

a. Each IRB shall have at least five (5) members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall, therefore, include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

b. Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

c. Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in non-scientific areas.

d. Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

e. No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

f. An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

SUBPART C - IRB FUNCTIONS AND OPERATIONS

56.108 IRB FUNCTIONS AND OPERATIONS

In order to fulfill the requirements of these regulations, each IRB shall:

a. Follow written procedures: (1) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and, (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

b. Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or, (3) any suspension or termination of IRB approval.

Except when an expedited review procedure is used (see 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in non-scientific areas. In order for the research to be

approved, it shall receive the approval of a majority of those members present at the meeting.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130.)

56.109 IRB REVIEW OF RESEARCH

a. An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

b. An IRB shall require that information given to subjects as part of informed consent is in accordance with 50.25. The IRB may require that information, in addition to that specifically mentioned in 50.25, be given to the subjects when in the IRB's judgement, the information would meaningfully add to the protection of the rights and welfare of the subject.

c. An IRB shall require documentation of informed consent in accordance with 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

d. An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond to persons in writing.

e. An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than

once per year, and shall have authority to observe or have a third party observe the consent process and the research.

56.110 EXPEDITED REVIEW PROCEDURES FOR CERTAIN KINDS OF RESEARCH INVOLVING NO MORE THAN MINIMAL RISK, AND FOR MINOR CHANGES IN APPROVED RESEARCH

a. The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the Federal Register.

b. An IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited review procedure set forth in 56.108(c).

c. Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

d. The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

56.111 CRITERIA FOR IRB APPROVAL OF RESEARCH

a. In order to approve research covered by these regulations, the IRB shall determine that all of the following requirements are satisfied:

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

treatment purposes.

2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example,the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by Part 50.

5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.

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

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

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

56.112 REVIEW BY INSTITUTION

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

56.113 SUSPENSION OR TERMINATION OF IRB APPROVAL OF RESEARCH

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

56.114 COOPERATIVE RESEARCH

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

SUBPART D - RECORDS AND REPORTS:

56.115 IRB RECORDS

a. An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolutions.

3) Records of continuing review activities.

4) Copies of all correspondence between the IRB and the investigators.

5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

6) Written procedures for the IRB as required by 56.108 (a) and (b).

7) Statements of significant new findings provided to subjects, as required by 50.25.

b. The records required by this regulation shall be retained for at least three (3) years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

c. The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

(Information collection requirements in this section were approved by the Office of Management and Budget [OMB] and assigned OMB control number 0910-0130.)