CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

TITLE: PHASE IV PROTOCOL OF GLUCOPHAGE (NDA 20-357)

DATE: 10/9/97

COMPARATIVE OUTCOMES STUDY OF METFORMIN INTERVENTION versus CONVENTIONAL APPROACH: The COSMIC Approach Study

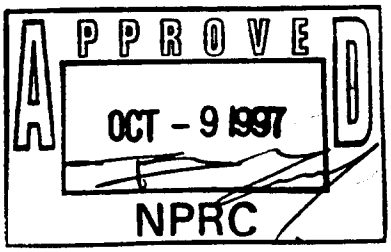

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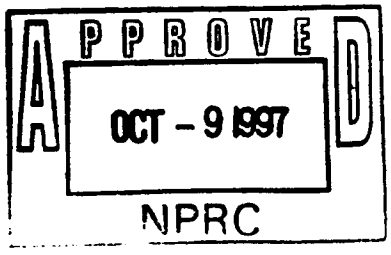
TABLE OF CONTENTS



I. SUMMARY

A. Purpose

The primary objective of this study is to compare the long-term (one year) serious adverse event profile of Glucophage® brand of metformin hydrochloride (hereafter referred to as metformin, either as monotherapy or in combination with a sulfonylurea) to that of a conventional approach, i.e., usual care, in patients with non-insulin dependent diabetes mellitus (NIDDM). A serious adverse event is one which meets any one of the following criteria: fatal or life-threatening, permanently or substantially disabling, requiring or prolonging inpatient hospitalization, a congenital anomaly, cancer, or an overdose. Usual care includes the use of sulfonylureas and/or insulin (in addition to diet), as is the customary treatment of NIDDM by the individual investigator.

B. Design

This is a multicenter, prospective, randomized, comparative, parallel design, open-label, long-term (one year) surveillance study of serious adverse events. Eligible patients will be randomized to either metformin (metformin or metformin plus a sulfonylurea) or usual care (sulfonylurea and/or insulin), in addition to diet, in a 4:1 allocation, with four times as many patients allocated to metformin as to usual care.

C. Patient Population

Approximately 10,000 male or female NIDDM patients, ≥ 18 years of age, who have failed on diet or are suboptimally responsive to sulfonylurea therapy will be enrolled. These patients must have normal renal function as defined by serum creatinine < 1.5 mg/dL for males and < 1.4 mg/dL for females, or normal creatinine clearance to be entered into the study. Women who are not post-menopausal must be non-lactating, incapable of becoming pregnant or if of childbearing potential, must be using an effective method of contraception. Patients with any contraindication to the use of metformin or oral sulfonylureas or insulin will be excluded from the study. A broad geographic representation of practicing physician specialists and generalists will be enrolling NIDDM patients.

Qualifying patients will have given written informed consent prior to screening. Patients must have NIDDM and must be either suboptimally controlled by diet alone or suboptimally controlled by sulfonylurea monotherapy.

At approximately 200 sites participating in this protocol substudy, a minimum of 570 patients (4:1, metformin to usual care) will have blood drawn for plasma lactate determination at month 12.

D. **Drug Administration**

Qualifying patients will be randomly assigned to treatment with metformin or to usual care. Randomization will occur when the site calls Corning PACT at 1-800-321-2330. Medications (metformin or usual care) will be prescribed and administered in accordance with the label, with dose adjustments made as clinically indicated.

Patients randomized to metformin and who are inadequately controlled on a diet alone will be treated with metformin alone. Patients will be prescribed according to the drug label, e.g., metformin 500 mg BID given with the morning and evening meals. Dosage can be increased to achieve glycemic control with one tablet every week, given with meals in divided doses, to a maximum of 2500 mg per day. Metformin can be administered twice a day up to 2000 mg per day (e.g., 1000 mg BID with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given TID with meals.

Patients randomized to metformin and who were inadequately controlled on a sulfonylurea will be treated with metformin plus continuing the current dosage of sulfonylurea therapy.

Patients randomized to usual care and who were inadequately controlled on a diet alone will be treated with conventional oral therapy (sulfonylurea).

Patients randomized to usual care and who were inadequately controlled on a sulfonylurea will be treated with either continued sulfonylurea monotherapy, insulin monotherapy, or sulfonylurea plus insulin therapy.

The brand of the oral sulfonylurea or the type of insulin is the choice of the individual investigator.

E. **Outcomes Evaluation**

The intent of this study is to obtain information on the serious adverse event profile associated with the use of metformin relative to usual care of NIDDM patients in everyday medical practice.

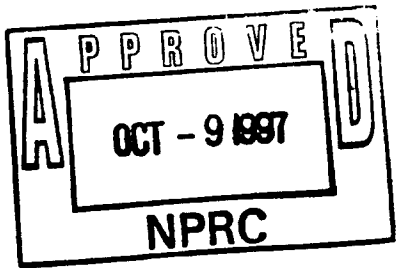
The outcomes which will be measured are:

- hospitalization for lactic acidosis
- hospitalization for metabolic cause
- all cause hospitalizations
- death due to lactic acidosis
- all cause death
- severe hypoglycemia requiring medical intervention
- all serious adverse events
- plasma lactate (Substudy sites only)

F. **Safety Evaluation**

Serious adverse events which occur during the study, whether or not related to the study drug (metformin or usual care), must be reported immediately by the investigator to Corning PACT (the contract research organization delegated the responsibility of managing this trial) , for prompt reporting to Bristol-Myers Squibb and to the FDA, as required.

All patients will be instructed to contact the investigator if a significant medical event occurs, so that appropriate action can be taken, or if they discontinue the study medication for any reason.



I. INTRODUCTION

Non-insulin-dependent diabetes mellitus (NIDDM) is a major health problem in the United States, and the fourth leading cause of death by disease. The prevalence of NIDDM in the United States is estimated to be over 14 million, although half of these individuals remain undiagnosed. The hyperglycemia of NIDDM may be controlled adequately by diet and exercise in about half of diagnosed patients. In overweight patients, weight reduction is also necessary. Unfortunately, limited patient acceptance and compliance reduces the utility of such an approach and, thereby, necessitates pharmacologic intervention for many patients.

Metformin is an oral antihyperglycemic agent that improves glucose tolerance in patients with NIDDM. Until the introduction of metformin to the U.S. market, sulfonylureas were the only oral hypoglycemic agents available for use in the treatment of NIDDM. Lowering of blood glucose by sulfonylureas in both normal individuals and Type II diabetics is achieved initially through enhanced endogenous insulin release, although, increased peripheral insulin responsiveness has also been described [1,2]. Sulfonylureas may cause hypoglycemia, occasionally severe and prolonged, in both Type II diabetics and nondiabetic individuals. Mild side effects of sulfonylureas include minor gastrointestinal distress, allergic dermatitis and disulfiram-like reactions after alcohol intake. Of a more serious nature is the potential for hepatotoxicity, ranging from impaired liver function to sever cholestatic jaundice, and unpredictable hematologic toxicity. Hematologic toxicity is occasionally fatal and may include granulocytopenia and agranulocytosis, red cell aplasia, thrombocytopenia, immune-mediated hemolytic anemia and pancytopenia with bone marrow aplasia. Chlorpropamide may also potentiate antidiuretic hormone action in the kidney, resulting in water retention, dilutional hyponatremia, and worsening of congestive heart failure [2,3].

Metformin, a biguanide, is in another chemical class of orally active hypoglycemic agents which, in contrast to the sulfonylureas, do not lower blood glucose by stimulation of endogenous insulin release. Metformin lowers blood glucose primarily by decreasing hepatic glucose production through either an effect on glycogenolysis or gluconeogenesis (or possibly both). An effect on glucose absorption as well as enhanced peripheral glucose uptake have also been evoked. Metformin appears to act at either the insulin receptor or at the post-receptor level, or both, to enhance the effectiveness of insulin. Thus, with metformin treatment, an actual **decrease** in fasting insulin levels may occur. Metformin is not, strictly speaking, a hypoglycemic agent, since it lowers **elevated** blood glucose levels in patients with Type II diabetes but does not have any effect on blood glucose levels in nonfasted, normal, nondiabetic individuals. In contrast to sulfonylureas and insulin, metformin monotherapy does not cause hypoglycemic crises in humans [4,5].

Metformin has been in clinical use for more than 30 years and is currently commercially available in more than 80 countries worldwide, including all major western European and Scandinavian countries and Canada. Glucophage® brand of metformin hydrochloride has never been withdrawn from any commercial market for either safety or efficacy reasons. In fact, use of metformin is increasing in many countries and its pharmacologic properties continue to be of considerable interest, from both a clinical and basic science perspective.

Mild adverse reactions reported in association with metformin therapy in controlled clinical trials include transient gastrointestinal disturbances, consisting primarily of diarrhea and nausea, which may occur in as many as 30% of patients during the initial weeks of treatment and contribute to the rationale of starting at a low dose of metformin [6,7]. Asymptomatic decreases in serum vitamin B_{12} levels have been seen in up to 12% of subjects in controlled clinical trials of six months duration [6,7].

As is the case for all biguanides, metformin use has been associated with the occurrence of lactic acidosis. However, the incidence of such occurrence is vastly different among the biguanides, with metformin having the lowest incidence of any biguanide which is or has been commercially available [8,11].

All cases of lactic acidosis reported in patients taking metformin have occurred in the setting of at least one or more acute or chronic illnesses, known to be either **direct** risk factors for the development of lactic acidosis in such patients (e.g., acute or chronic renal impairment with resultant metformin accumulation and including acute renal dysfunction that may occur with intravascular contrast media during radiologic studies in diabetics) or **independent** risk factors for lactic acidosis (acute or chronic cardiovascular disease, pulmonary disease with hypoxia, sepsis or acute or chronic hepatic disease with or without associated alcoholism) [12]. Thus, the risk of occurrence of lactic acidosis in patients taking metformin can be minimized by heeding the recognized contraindications to its use.

Metformin use in France since 1984 (when adverse event reporting was mandated), accounts for approximately 2.5 million patient-years of exposure to metformin. Per 1,000 patient-years of exposure, there has been an average of 0.03 reported cases of lactic acidosis, with 0.015 fatal cases per 1,000 patient-years.

Similarly, in Sweden, where very careful adverse event reporting and metformin usage information is available, a very similar incidence rate has been reported (0.024 cases per 1,000 patient-years) over the five year period 1987-1991, with 0.012 fatalities directly attributable to the acidosis per 1,000 patient-years [13]. (For purposes of comparison, it should be noted that at the time of phenformin's withdrawal from most world markets,

FDA estimates of phenformin-associated lactic acidosis in the U.S. varied from 0.25 to 4.0 cases per 1,000 patient-years, with a mortality rate of from 0.125 to 2.0 per 1,000 patient-years [14]).

Furthermore, many of the cases of lactic acidosis temporally associated with metformin use lack supportive evidence (i.e., elevated blood metformin levels consistent with metformin accumulation) to unequivocally establish causality and, thus, the incidence may be even less than these figures suggest [15].

Finally, it should be recalled that the incidence of serious hypoglycemia with sulfonylureas is greater than the incidence of lactic acidosis in patients receiving metformin, while the estimated mortality risks of the sulfonylureas and metformin, for this respective side-effect, are almost identical [9-11].

It is widely accepted that assessment of adverse event incidence based on spontaneous adverse event reporting is affected by under-reporting (perhaps by a factor of 10). Until the present, use of metformin in the United States has been limited to clinical trials conducted in selected patient populations. No cases of lactic acidosis have been observed during the course of those trials. Since the patient population receiving metformin in the United States will be large and will include many patients with various concomitant health problems, a postmarketing surveillance study of serious adverse events will be conducted to confirm metformin's safety in a more heterogeneous population.

The current proposal, therefore, seeks to obtain additional relevant safety information on the occurrence of serious adverse events in association with metformin use in a prospective fashion in a representative U.S. patient population, through the conduct of this large scale simplified clinical trial.

III. PURPOSE

The primary objective of this study is to compare the long-term (one year) serious adverse event profile of Glucophage® brand of metformin hydrochloride (hereafter referred to as metformin, either as monotherapy or in combination with a sulfonylurea) to that of a conventional approach, i.e., usual care, in patients with non-insulin dependent diabetes mellitus (NIDDM). A secondary objective is to compare plasma lactate levels following 12 months of metformin therapy to those exhibited by the usual care group. Selected sites will participate in a substudy to collect plasma for lactate determination. A serious adverse event is one which meets any one of the following criteria: fatal or life-threatening, permanently or substantially disabling, requiring or

prolonging inpatient hospitalization, a congenital anomaly, cancer, or an overdose. Usual care includes the use of sulfonylureas and/or insulin (in addition to diet), as is the customary treatment of NIDDM by the individual investigator.

IV. PATIENT POPULATION

Approximately 10,000 patients with non-drug treated NIDDM, or patients with established, drug-treated NIDDM (on sulfonylurea monotherapy), will participate after providing written informed consent. Patients will be eligible if their hyperglycemia is not adequately controlled by diet alone or by diet and their present oral sulfonylurea therapy. In all cases, eligibility will be in accord with metformin and usual care labeling.

A. Inclusion Criteria

1. Patients must have documented NIDDM (Type II diabetes) and must be either:

   a. currently suboptimally controlled on diet alone; **or**
   b. currently suboptimally controlled on sulfonylurea monotherapy.

2. Patients must be 18 years of age or older;

3. Both men and women are eligible to participate. Women who are not postmenopausal must be non-lactating, incapable of becoming pregnant or, if of childbearing potential, must be practicing an effective method of contraception. Standard birth control methods are considered to be sterilization, oral or implanted contraceptive therapy, intra-uterine devices, use of a diaphragm in combination with contraceptive cream, jelly, or foam, or partner's use of a condom in combination with a contraceptive cream, jelly, or foam. Women of child-bearing potential should be instructed to notify the investigator of any delay or missed menses or any changes in birth control method;

4. Patients should demonstrate normal renal function as defined by serum creatinine of < 1.5 mg/dL for males and < 1.4 mg/dL for females, or normal creatinine clearance;

5. Patients should be able in acceptable health in the judgement of the clinical investigator, on the basis of interview, medical history, physical exam, and usual urine and lab tests (consistent with the labeling of metformin or usual care therapy);

6. Signed, witnessed, written informed consent must be obtained;

7. Patients must be able to comply with the requirements of the study (have the capacity to speak and comprehend the English language, and have access to the use of a telephone).

B. **Exclusion Criteria**

Patients will be excluded from the study if they have any contraindications to the use of either metformin, oral sulfonylureas, or insulin, including the following:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males] and ≥ 1.4 mg/dL [females]) or abnormal creatinine clearance;

2. Known hypersensitivity to either biguanides or sulfonylureas or insulin, or any components of the formulations;

3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma;

4. Females of childbearing potential who are not using an effective form of contraception, as described above, or females who are pregnant or nursing;

5. Patients previously enrolled into this protocol.

V. PATIENT CONSENT

Signed and dated written informed consent must be obtained by the investigator from the patient after full disclosure of the potential risks and their nature. Consent must be obtained before a prospective study candidate participates in any study-related procedure, including any change in current therapy required for entry into the study.

The fact that such consent was obtained must be recorded in the case report form.

A statement of policy concerning informed consent, extracted from the Code of Federal Regulation is included as Appendix A of this protocol. Forms used to obtain consent must conform to these regulations.

All females of child-bearing potential should be informed that they should consult promptly with the investigator of any menstrual irregularity.

VI. DRUG SUPPLIES

A. Description and Dispensing Instructions

Qualifying patients will be randomly assigned to treatment with metformin or to usual care. Randomization will occur when the site calls Corning PACT at 1-800-321-2330. Medications (metformin or usual care) will be prescribed and administered in accordance with the label, with dose adjustments made as clinically indicated.

Patients randomized to metformin and who are inadequately controlled on a diet alone will be treated with metformin alone. Patients will be prescribed according to the drug label, e.g., metformin 500 mg BID given with the morning and evening meals. Dosage can be gradually increased to achieve glycemic control with one tablet every week, given with meals in divided doses, to a maximum of 2500 mg per day. Metformin can be administered twice a day up to 2000 mg per day (e.g., 1000 mg BID with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given TID with meals.

Patients randomized to metformin and who were inadequately controlled on a sulfonylurea will be treated with metformin plus continuing the current dosage of sulfonylurea therapy.

Patients randomized to usual care and who were inadequately controlled on a diet alone will be treated with conventional oral therapy (sulfonylurea).

Patients randomized to usual care and who were inadequately controlled on a sulfonylurea will be treated with either continued sulfonylurea monotherapy, insulin monotherapy, or sulfonylurea plus insulin therapy.

The brand of the oral sulfonylurea or the type of insulin is the choice of the individual investigator.

VII. STUDY PLAN

A. General Considerations

This is a multicenter, prospective, randomized, comparative, parallel design, open-label study. Approximately 10,000 patients with NIDDM, ≥ 18 years of age will be randomized 4:1 to metformin or usual care (sulfonylurea and/or insulin, in addition to diet) and followed for 1 year of treatment. Metformin therapy will either be monotherapy or in combination with a sulfonylurea.

This study will monitor the serious adverse event (an event that meets any one of the following criteria: fatal or life-threatening, permanently or substantially disabling, requiring or prolonging inpatient hospitalization, a congenital anomaly, cancer, or an overdose of medication) profile associated with the use of metformin, when given either as monotherapy or in combination with sulfonylureas, and other usual care blood glucose-lowering therapy in NIDDM patients over a one year period. Physicians will follow their routine practices in monitoring these patients.

Patients will be asked to make two physician office visits: one at enrollment, one after three months. In addition, telephone interviews with the patients (or next of kin) will occur at months 6, 9, and 12, to obtain information about study drug treatment, concomitant medications, and to specifically identify any serious adverse event (including hospitalizations), severe hypoglycemic episodes (defined as an event with symptoms consistent with hypoglycemia in which the person requires assistance of another person, is comatose, or has a seizure and which is associated with a blood glucose level below 50 mg/dL) requiring medication intervention, or deaths that may have occurred. Relevant information from non-protocol mandated patient contacts with the physician will also be relayed to Corning PACT.

At selected sites patients will be asked to make three office visits; one at enrollment, one after three months and one after twelve months of treatment for collection of plasma for lactate determination. As outlined above, telephone interviews with the patients (or next of kin) will also occur at months 6, 9 and

12.

Patients will be provided with a one-year Patient Diary, in which to record the occurrence of any significant medical events, hospitalizations, and/or severe hypoglycemic episodes requiring medical intervention, as well as concomitant medications.

All patients will be followed for a period of 12 months, even if the assigned therapy is changed or discontinued, except in the event that premature termination was on the basis of withdrawal of consent by the patient. An effort must be made to determine why a patient fails to return for a scheduled visit or has decided to prematurely terminate participation. The reasons for such premature termination must be supplied in the patient's case report form.

Hospital records and death certificates will be requested and reviewed and all serious adverse events will be fully evaluated.

In the event that a patient is determined to be pregnant during the study, it is advised that oral antidiabetic therapy (metformin, sulfonylurea) be ***promptly*** discontinued and the patient managed with insulin or other appropriate therapy. **Any pregnancies that occur during the course of the study must be reported to the Corning PACT monitor and the patient must be followed by the investigator. The outcome of the pregnancy and the status of the newborn must also be reported to Corning PACT. Neonates must be followed up for ≥ 8 weeks.**

B. **Concomitant Therapies**

All concomitant medication usage, including the reason for use, date started, total daily dose, and date discontinued, will be recorded on the case report form.

C. **Precautions to Minimize Risk**

For patients randomized to **metformin** therapy, precautions as described in the package insert should be observed.

For patients randomized to **usual care**, precautions as described in the package insert(s) of the drug therapy(ies) being employed, should be observed.

D. **Diet/Exercise Restrictions**

Patients should be instructed to maintain their recommended dietary patterns and restrictions and level of exercise throughout the study. Patients should not be encouraged to undergo significant modifications in lifestyle (i.e., start a weight reduction program or exercise program) or diet during the course of the study.

E. **Sequence of Events**

1. **Visit One (Study Enrollment Visit)**

At the study enrollment visit, the investigator will evaluate each patient against the inclusion and exclusion criteria. Eligible patients will be asked to enroll in the study, and written informed consent will be obtained.

The investigator will obtain and record on the case report form (CRF) the following information:

- patient demographics;
- physical examination (including height, weight, and vital signs);
- medical history (including detailed diabetes history, current treatment of diabetes, alcohol and tobacco use and description of concomitant illnesses);
- concomitant medication usage;
- indication that the patient fulfills all inclusion and none of the exclusion criteria requirements;
- corresponding CRF pages for visit One will be transmitted by the investigator to Corning PACT.

The investigator will telephone Corning PACT at **1-800-321-2330** to enroll each patient in the telephone interviewing program. At this time, the patient will also identify a secondary contact (e.g., next of kin) who may be contacted in the event contact cannot be made directly with the patient.

Patients will be randomized, the open-label therapy (metformin vs usual care) will be accordingly prescribed, and the study medication information will be entered onto the CRF.

Patients will be enrolled into the study in a sequential manner at each site. Each patient will have a unique patient identification number which will consist of a four-digit investigator number (0001, 0002, 0003, etc.), followed by a hyphen and a two-digit patient number (01, 02, 03, etc.). Thus, as an example, for the 17th patient enrolled for Investigator 0124, the complete patient identification number would be 0124-17.

Patients will be provided with a one-year Patient Diary for recording the occurrence of any significant medical events, hospitalizations, and/or severe hypoglycemic episodes, as well as concomitant medications. The diary is being provided solely to serve as a memory aid to the patients when health -related information is solicited at the 3 month office visit and during the telephone interviews, described below, but will not be retrieved or utilized in the data analysis.

Patients will also be instructed to contact the physician's office if they experience any problems during the study, if they discontinue their assigned study medications, and to provide information on any serious adverse event(s) they experience.

2. **Visit Two (Follow-Up Evaluation, Month 3):**

Three months after the patient is enrolled in the study, an interim **physician visit** will take place.

At this visit, the physician will document the following information on the CRF:

- physical examination;
- all reported **SERIOUS** adverse events, including hospitalizations;
- severe hypoglycemic episodes (defined as an event with symptoms consistent with hypoglycemia in which the person requires assistance of another person, is comatose, or has a seizure **and** which is associated with a blood glucose level below 50mg/dL) requiring intervention;
- concomitant medications;
- current study therapy;
- corresponding CRF pages will be transmitted by the investigator

to Corning PACT.

3. **Patient Follow-Up Via Telephone Monitoring (Months 6, 9 and 12):**

Patients will be contacted at months 6,9 and 12, by the Telephone Interview Coordinating Center for follow-up information concerning their health status, study drug use, use of concomitant medications, the occurrence of any serious adverse events including hospitalizations, and/or severe hypoglycemic episodes requiring medical intervention.

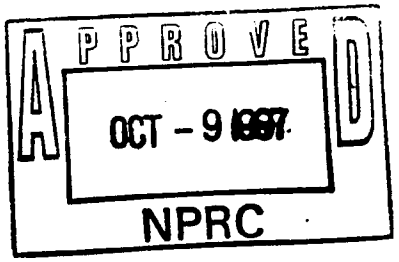
4. Visit Three (Phlebotomy, Month 12) [Substudy sites only]:

Patients will be seen at month 12 and have blood drawn for a plasma lactate determination.

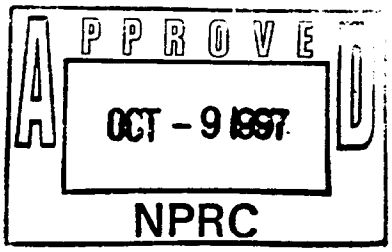
5. **Unscheduled Visits and/or Contacts with the Investigator**

At each patient visit which has been scheduled according to the physician's routine practice (i.e., visits that are not protocol mandated) and at any unscheduled visit or telephone contact with the patient or next of kin, the investigator will obtain updated information regarding any changes in health status, study drug therapy, concomitant medications, and the occurrence of any serious adverse events or severe hypoglycemic episodes requiring medical intervention. The investigator will document on the CRF:

- all reported **SERIOUS** adverse events, including hospitalizations;
- severe hypoglycemic episodes requiring medical intervention;
- concomitant medications;
- current study therapy.



F. Study Schema



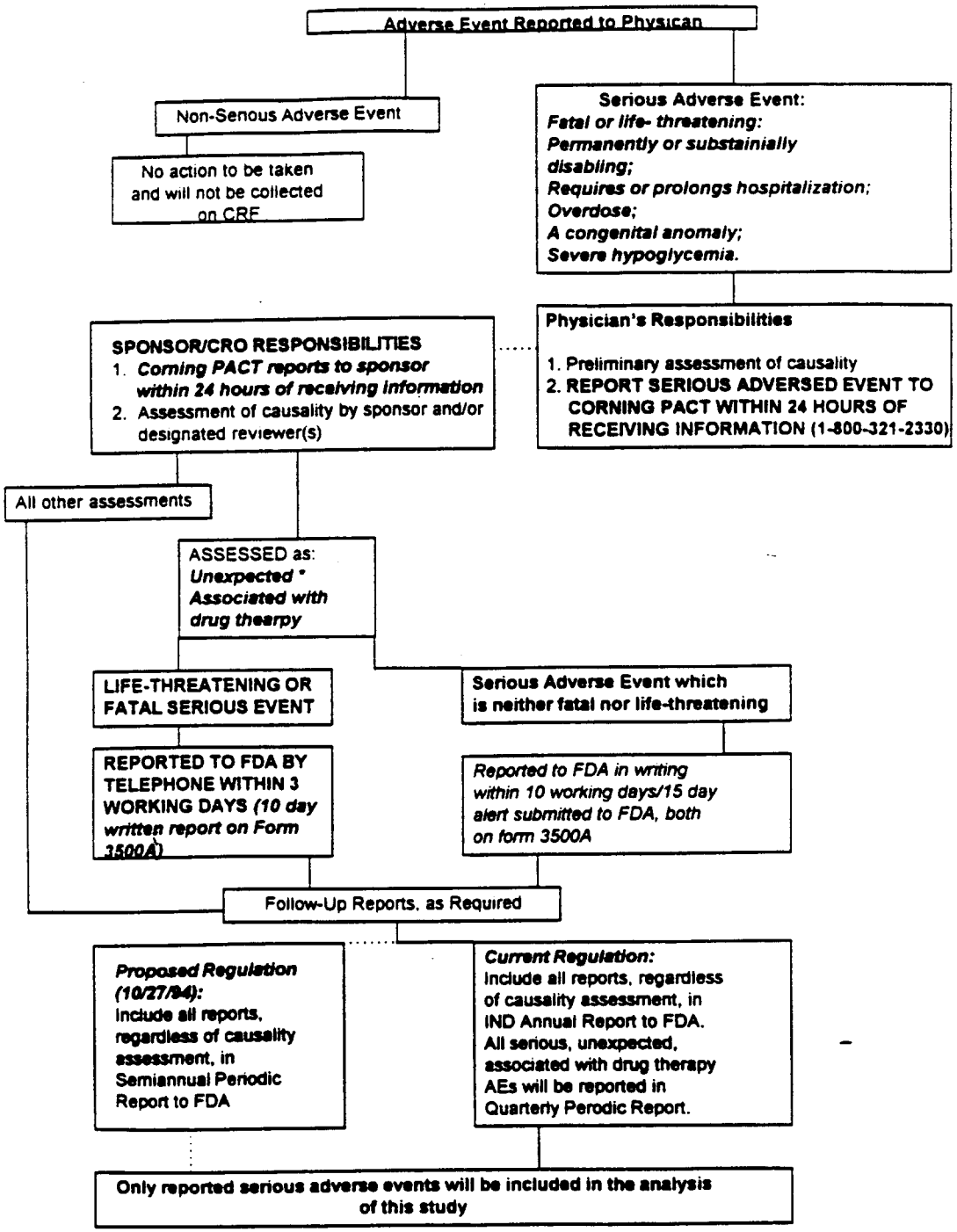
G. Schedule of Events

	Study Enrollment Visit/ Randomization	Physician Follow-Up Visit	Telephone Interviews By Corning PACT/TICC*			Follow-Up Visit (Addendum Sites)
Visit	1	2	3	4	5	6
Month	0	3	6	9	12	12
Informed Consent	X					
Medical History	X					
Physical Examination	X	X				
Vital Signs	X	X				
Body Weight and Height	X	X				
Plasma Lactate Level						X
Randomization Assigned by Corning PACT	X					
Record Concomitant Medication Usage	X	X	X	X	X	
Update of Safety-Related Information**		X	X	X	X	

* TICC = Telephone Interview Coordinating Center

** To include current study drug therapy, serious adverse events (including hospitalizations), and severe hypoglycemic episodes requiring medical intervention. **NOTE**: All serious adverse events must be reported to Corning PACT within 24 hours of receipt of such information. Phone 1-800-321-2330.

H. Serious Adverse Event Reporting Schema



* Serious expected reports will be captured in the periodic report.

I. Laboratory Procedures

Patients at selected sites will have their blood drawn for plasma lactate determination at or after 12 months of treatment (visit three). Blood will be collected in pre-chilled tubes containing fluoride and centrifuged immediately. The plasma will be removed and frozen immediately. Samples will be transported to a central laboratory on dry ice. Plasma lactate will be measured by an enzymatic assay utilizing NAD^+ and lactate dehydrogenase.

VIII. CRITERIA FOR DISCONTINUING THERAPY

Patients may choose to withdraw, or may be withdrawn from the study at the discretion of either the investigator or the sponsor, for any reason, at any time. All prematurely terminated patients will continue to be followed by TICC for Corning PACT for one year, except when patients have withdrawn informed consent.

If the patients should withdraw because of an adverse event, and if considered **serious**, then the adverse event should be reported as described in Section IX.

All **serious adverse events** resulting in the discontinuation (temporary or permanent) of study drug should be followed until resolution, stabilization, or determination that the serious adverse event is/was not considered to be related to the study medication.

As previously noted, an effort must be made to determine why a patient fails to return for a scheduled visit.

The investigator must provide information about the reason for the premature discontinuation on the appropriate page(s) of the CRF.

Any pregnancies that occur during the course of the study must be reported to the Corning PACT monitor and the patient must be followed by the investigator. The outcome of the pregnancy and the status of the newborn must also be reported to Corning PACT. Neonates must be followed up for ≥ 8 weeks.

Information provided to Corning PACT will be relayed to Bristol-Myers Squibb.

A. Procedures for Patients with Suspected Lactic Acidosis

In order to ensure that all cases of lactic acidosis are identified, investigators will be provided with a suggested procedure for the diagnosis and treatment of lactic acidosis, consistent with the labeling for Glucophage®, as follows:

Lactic acidosis is a rare, but serious metabolic complication which can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases.

Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia.

Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

As noted previously, the reported incidence of lactic acidosis in patients receiving metformin hydrochloride is rare (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.