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NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

Better Health Through Responsible Self-Medication

April 15, 1994

Docket Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: OTC Dockets No. 81N-0022 and 76N-052N

TO WHOM IT MAY CONCERN:

Enclosed is the original and three copies of the epidemiologic study protocol entitled "Hemorrhagic Stroke Project: Case-Control Study of PPA and Hemorrhagic Stroke."

Copies of this protocol have been forwarded to individuals within the Agency as noted below.

Please sign the enclosed form that confirms receipt of this submission.

Sincerely yours,

R. William Soller Ph.D.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Enclosures: "Hemorrhagic Stroke Project: Case-Control Study of PPA and Hemorrhagic Stroke" (original and three copies)

Receipt Verification Slip

cc: Michael Weintraub, M.D.
Joel P. Freiman, M.D.

WS:jq

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DOCKETS MANAGEMENT BRANCH

81N-0022

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HEMORRHAGIC STROKE PROJECT:

CASE-CONTROL STUDY OF PPA AND HEMORRHAGIC STROKE

Submitted to
Nonprescription Drug Manufacturers Association
April 1994

HEMORRHAGIC STROKE PROJECT:
CASE-CONTROL STUDY OF PPA AND HEMORRHAGIC STROKE

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Hemorrhagic Stroke Project:
Case-Control Study of PPA and Hemorrhagic Stroke

Table of Contents

A. Introduction and Rationale

The accumulation of adverse drug events and case series reports has led to some concern that products containing phenylpropanolamine increase the risk for hemorrhagic stroke (1-11). Although no controlled scientific evidence exists to support this worry, the manufacturers of products containing phenylpropanolamine have joined together with the Food and Drug Administration in planning a program of research to clarify whether any increase in risk does exist.

The preferred research strategy for assessing the risk of hemorrhagic stroke in phenylpropanolamine users compared to non-users is a prospective or cohort study. Despite its scientific advantages, a cohort study with concurrent subject follow-up would not provide timely results useful for regulatory and public health policy. Furthermore, the logistics and costs of such a study would be formidable owing to the unavoidably large numbers of patients required to detect differences in the rate of hemorrhagic stroke between phenylpropanolamine users and non-users.

When a disease is very rare, as is the situation with phenylpropanolamine use and hemorrhagic stroke, the case-control study is an efficient alternative to the observational cohort study (12). Properly designed and conducted, the case-control strategy can provide a valid and scientifically useful estimate of the risk between an exposure such as phenylpropanolamine and a rare outcome such as hemorrhagic stroke. In the design of the Hemorrhagic Stroke Study, we have taken great care to minimize sources of potential bias in the assessment of this relationship. In particular, to the extent possible we have used a

population-based sampling strategy to minimize any selection bias in the choice of cases and controls; used matching and analytical methods to minimize susceptibility bias; and proposed state-of-the-art techniques to achieve equality in recollection of exposure to phenylpropanolamine containing products.

In the next section, we present a general overview of the study. Thereafter, we shall discuss the methodologic details that will guide the conduct of the research. As part of that discussion, we review the considerations in design just outlined that are crucial to the study's scientific validity and clinical applicability.

B. Objectives and Specific Aims

The overall objective of the research is to conduct a valid epidemiologic investigation assessing the relationship between the use of products containing phenylpropanolamine (as appetite suppressants and cough/cold remedies) and the subsequent risk of hemorrhagic stroke. (We recognize that phenylpropanolamine is also prescribed for the management of stress incontinence. Although less common than its over-the-counter use, we shall also monitor all prescription use of phenylpropanolamine.) In the target population of 18-49 years of age, hemorrhagic stroke is a rare disorder, and a forwardly-directed observational cohort study is not feasible. Instead, the proposed research has been designed as a case-control study with explicit procedures intended to ensure the validity and applicability of the study results.

The proposed study has the following coequal and primary aims:

1. To determine whether phenylpropanolamine users ages 18-49, compared to non-users, have an increased risk of hemorrhagic stroke.

2. To estimate the association between phenylpropanolamine and hemorrhagic stroke separately by the non-prescription indications for

phenylpropanolamine use: appetite suppressant or cough/cold remedy; and by the use of appetite suppressants in women ages 18-49.

3. To estimate the association between "first dose" use of phenylpropanolamine (either cough/cold or appetite suppressant) and hemorrhagic stroke in women ages 18-49.

C. General Overview of Study

The Hemorrhagic Stroke Study will use a hospital-based sampling strategy to assemble cases and controls for this investigation. The study will be conducted among a network of 20 (of the 36) short-term hospitals in the State of Connecticut that account for nearly 80% of all stroke admissions, and among a network of participating hospitals in Providence, Rhode Island, Cincinnati, Ohio, and Houston, Texas. Eligible cases (and their matched controls) will be enrolled within 14 days of the stroke event.

The outcome event that defines case status is hemorrhagic stroke. Subjects with suspected hemorrhagic stroke will be identified through a system of active surveillance at each of the participating hospitals. All diagnoses will be confirmed, before enrollment, by one of five physician investigators (Lawrence Brass, Thomas Brott, Edward Feldman, James Grotta, Walter Kernan) blind to knowledge of phenylpropanolamine use. An expert panel of three stroke neurologists will later review and validate the diagnosis for each subject (details of the case validation are described in Section 3).

The patient's exposure status will be determined from direct interview with confirmation by examination of bottles and other product containers. To answer the first and third specific aims, we shall examine all use of PPA. The second aim requires that PPA exposure be classified separately by its non-prescription indication for use. The

exposure interval will also depend on the specific aim being studied. The analyses for the first and second specific aim will be based on a three-day exposure window, while the analysis for the third specific aim depends only on first day/first dose exposure. (Additional analyses will also take account of time from last and first use of phenylpropanolamine, and the impact of recency of use. This latter effect will be estimated by examining intervals from last use, such as <24 hours, 24-<48 hours, 48-<72 hours, etc.) Risks of hemorrhagic stroke in users compared to non-users will be estimated with the odds ratio, adjusted for potential confounding (susceptibility) features.

D. Experimental Design and Methods

1. Active Surveillance Program

The purpose of the active surveillance program is to ensure that the research team is notified of every occurrence of hemorrhagic stroke in individuals ages 18-49 within the surveillance system. To achieve this aim the surveillance program consists of two components. The first is a network of short-term hospitals. The second component is a surveillance team consisting of the study's neurologists and the research staff at each location. Because the surveillance program was developed first for the Connecticut site we shall describe this network in detail.

a) Connecticut Surveillance Program

1) Connecticut Hospital Network

To assemble the Connecticut-based hospital network for the Hemorrhagic Stroke Study, we first needed to obtain data on the number of hemorrhagic stroke discharges from acute care hospitals in the State of Connecticut. This was accomplished with the cooperation of the Connecticut Health Information Management Exchange (CHIME system). CHIME maintains a state-wide data base of clinical records submitted by

Connecticut's 36 short-term hospitals. By searching the data base for 1987-89, we established the following information for men and women ages 18-49 who were discharged alive with a principal diagnosis of hemorrhagic stroke (ICD-9-CM codes 430-432).

PERSONS AGES 18-49 WITH PRINCIPAL DISCHARGE DIAGNOSIS 430-432

Discharge Diagnosis 1987-1988	Number
430 (subarachnoid hemorrhage)	76
431 (intracerebral hemorrhage)	53
432 (other hemorrhage)	16
Total	145
1988-1989	
430 (subarachnoid hemorrhage)	76
431 (intracerebral hemorrhage)	45
432 (other hemorrhage)	13
Total	134

These data reflect individuals discharged alive with a diagnosis of hemorrhagic stroke for all 36 short-term general hospitals in Connecticut. We next examined the distribution of stroke discharges in each year by the number of licensed beds per hospital.

DISCHARGES WITH PRINCIPAL DIAGNOSIS 430-432 BY HOSPITAL BED SIZE (LICENSED)

DISCHARGE DIAGNOSIS	0-175	176-250	251-475	>475	Total
FY 1987-88					
430	1	1	22	52	75
431	3	3	25	22	53
432	0	3	6	7	16
Total	4	7	53	81	145
FY 1988-89					
430	1	3	21	51	76
431	2	2	21	20	45
432	0	1	4	8	13
Total	3	6	46	79	134

The data in the preceding table establish the consistency of discharges by year, by diagnostic codes and by hospital bed number. In reviewing these data, we noted that the 20 hospitals with >250 licensed beds comprised 92% of all patients ages 18-49 discharged with hemorrhagic stroke in 1987-88, and 93% of all such individuals in 1988-89. We chose, therefore, to create the hospital surveillance network using these 20 institutions.

In the next table, the 20 hospitals are listed in alphabetical order, along with their licensed number of beds and Chief of Neurology.

CONNECTICUT HOSPITAL SURVEILLANCE NETWORK

Hospital	Beds	Chief of Neurology	Hospital	Beds	Chief of Neurology
Backus	260	Anis Racy	New Britain	432	Barry Spass
Bridgeport	597	Kanaga Sena	Norwalk	388	Robert Levine
Danbury	450	Jan Mashman	St. Francis	701	William Healey
Greenwich	296	Alan Rapoport	St. Joseph's	260	Evangelos Xistris
Griffin	261	James Butler	St. Mary's	347	A. Roger Bobowick
Hartford	850	Leslie Wolfson	St. Raphael's	491	Bruce Haak
Law. & Mem.	350	David Thompson	St. Vincent's	391	Kenneth Siegel
Manchester	303	Robert Berland	Stamford	305	Evangelos Xistris
Middlesex	380	Arthur Waldman	Waterbury	405	Steven Eisen
Mount Sinai	379	Gary Belt	Yale-N.H.	785	Stephen Waxman

2) Connecticut Surveillance Team

The surveillance team responsible for identifying cases of hemorrhagic stroke in Connecticut will include the following individuals: Study neurologist (Lawrence Brass); Field Director (TBN); data technicians/interviewers.

The surveillance officer at each hospital will be designated by the Chief of Neurology. We envision that the type of individual may be different depending on the hospital. For instance, at some hospitals the ideal person may be a neurology chief resident, or a neurology chief nurse. At other hospitals, the best individual may be the utilization

review or discharge planning specialist. In addition to a weekly phone contact with the surveillance officer, one of the data technicians will contact the admissions office weekly at each hospital to identify any patients admitted with a diagnosis of stroke.

As noted, each of these contacts will be made with each hospital once a week. This will ensure that new stroke admissions will be identified and eligible patients enrolled in a timely manner. Surveillance officers at each hospital will also be urged to contact the research team whenever a stroke patient is admitted to their hospital.

b) Surveillance Program in Providence, Rhode Island, Cincinnati, Ohio, and Houston, Texas

To ensure an adequate base population from which to sample cases and controls, we have identified three additional locations for subject identification. Each of the three sites has a designated Principal Investigator who is responsible for implementation of the protocol.

In Providence, there are 7 participating hospitals. The network in Cincinnati comprises 17 hospitals in the following counties: Boone, Campbell, Clermont, Hamilton, and Kenton. The table below lists the network hospitals for each geographic location. (Hospitals in Houston, Texas are to be named.)

NETWORK HOSPITALS FOR NON-CONNECTICUT GEOGRAPHIC LOCATIONS

PROVIDENCE, RHODE ISLAND	
Rhode Island Hospital	Kent County Hospital
Roger Williams Hospital	V.A. Medical Center
Miram Hospital	Pawtucket Memorial Hospital
St. Joseph Hospital	
CINCINNATI, OHIO	
Bethesda Oak Hospital	Our Lady of Mercy - Anderson
Bethesda North Hospital	Our Lady of Mercy - Clermont
The Christ Hospital	Our Lady of Mercy - Fairfield
Deaconess Hospital	Providence Hospital
Good Samaritan Hospital	St. Elizabeth Medical Center - North
Jewish Hospital	St. Elizabeth Medical Center - South
St. Francis/St. George	St. Luke Hospital - East
University of Cincinnati Medical Center	St. Luke Hospital - West
	Veterans Administration

2. Overall Eligibility Criteria for Cases and Controls

Potentially eligible subjects are men and women, ages 18-49, who meet all of the study requirements. For case and control selection, subjects will be ineligible if they have a history of previous stroke (hemorrhagic or ischemic), or transient ischemic attacks, or if they die or are unable to participate in the interview.

3. Criteria for Case Selection

One of the methodologic advantages of the study design for the Hemorrhagic Stroke Study is that all four sites have enrolled nearly all of the acute care hospitals in their metropolitan or geographic location. To ensure that the case series is representative of all hemorrhagic strokes among subjects 18-49 years, the research team needs to identify and enroll all possible cases of hemorrhagic stroke within the hospital network. Consequently, the surveillance team will enumerate all strokes (regardless of type) in age-pertinent subjects. Using the data from a screening questionnaire, one of the study physicians, without knowledge of medication use, will determine whether the subject meets the criteria for a hemorrhagic stroke as well as other eligibility criteria.

After subjects have been enrolled and all data on hospitalization collected, an independent panel of expert stroke neurologists, also without knowledge of medication history, will use strict clinical criteria to qualify subjects as hemorrhagic stroke prior to data analysis. Thus, the final case group may not include every patient enrolled by the study team. (A complete log of hemorrhagic stroke patients rejected by the study team will also be maintained and reviewed by the expert panel to search for "false-negative" decisions.)

a) Criteria for Hemorrhagic Stroke

The main purpose of the diagnostic criteria are to ensure the accurate identification of patients with stroke that is caused by brain hemorrhage. An additional purpose of the criteria is to classify patients with brain hemorrhage into the two distinctive subtypes of intracerebral hemorrhage or subarachnoid hemorrhage. The diagnostic criteria require a clinical syndrome compatible with stroke, and a set of characteristic findings on brain imaging with computed tomography (CT). When a CT scan is unavailable or non-diagnostic, findings from an MRI or lumbar puncture may substitute.

1) Clinical Stroke Syndrome

Stroke events present with a wide array of symptoms depending on their location within the brain, size, and pathophysiology. Since the symptoms and signs of stroke are well described in standard textbooks, we shall not repeat them here. For the purpose of this study, all patients must have signs and symptoms consistent with a stroke.

Although some symptoms and signs are more commonly associated with intracerebral hemorrhage than with ischemic stroke, none are suitably accurate for diagnosis or management. For that reason, the classification of stroke type depends upon brain imaging studies.

2) Findings on CT Scan

(All scans will be collected by the investigators and available for review.)

Intracerebral hemorrhage (ICH) will be diagnosed based on the finding of a homogeneous, hyperdense lesion in the subcortical white matter or deeper structures of the cerebral hemispheres that corresponds to the patient's symptoms and physical signs. Because some patients with ischemic infarction may subsequently develop transformation into

"hemorrhagic infarction", care must be taken to distinguish this from intracerebral hemorrhage. This distinction may be easy if there is a prominent mass effect (characteristic of intracerebral hemorrhage) or if the appearance of the high attenuation lesion is spotted or mottled (characteristic of hemorrhagic transformation). Hemorrhagic transformation in ischemic lesions does not occur immediately, so diagnostic uncertainty rarely occurs when patients undergo prompt evaluation.

Subarachnoid hemorrhage (SAH) will be diagnosed by the presence of a high intensity signal in the subarachnoid space.

3) Findings on MRI Scan

The gold standard for diagnosing intracerebral hemorrhage is the CT scan. The performance of MRI scanning has not been fully compared to CT, but a characteristic temporal pattern for the MRI appearance of hemorrhage stroke has been described. Hyperacute hematomas are hyperintense. By about 24 hours, however, hemorrhagic lesions become hypointense and stay that way for about 7 days. After 7 days, hemorrhagic lesions again become hyperintense.

Information on the MRI diagnosis of stroke is rapidly emerging. For now, CT is generally believed to be superior except for selected patients with posterior fossa lesions. MRI has a distinct role to play in cerebral angiography.

Diagnostic criteria for the Hemorrhagic Stroke Study will use MRI findings only when CT scanning is unavailable or non-diagnostic. In these two instances, MRI scans will be interpreted by an expert consultant in neuroradiology who will judge whether the MRI is diagnostic of hemorrhage. The consultant will be blind to patients' exposure status.

4) Diagnostic Criteria for Brain Hemorrhage, Site Uncertain

In a small proportion of patients with subarachnoid hemorrhage and a smaller proportion of patients with intracerebral hemorrhage, the CT scan or MRI may be normal. Only the CSF analysis will be diagnostic. Patients with brain hemorrhage from an uncertain site are generally considered to have SAH and will be eligible for the study if they have symptoms and signs of a stroke, no definitive corresponding lesion on CT scan or MRI, and a diagnostic lumbar puncture.

Criteria for a brain hemorrhage will be the presence of red cells (greater than 1000 per cubic millimeter) in two consecutive tubes of CSF. The concentration must not fall by more than 25% between tubes and xanthochromasia must be present. When the CSF contains blood or xanthochromasia (in a pattern that is not consistent with trauma from the tap), it is not possible to determine whether the source is SAH or ICH.

b) Case Enrollment

With approval of the case patient's physician, a member of the research team will discuss the study with the patient. After the study has been explained, if the patient is interested in participating, verbal consent will be obtained by the researcher. Arrangements will be made for a direct interview (by a study data technician) with the patient either in the hospital or in the patient's home. At that time, written authorization will be obtained for release of medical records.

c) Final Case Qualification by Panel of Experts

Final case qualification will be determined by a panel of expert stroke neurologists using predetermined criteria. The panel will be presented with all of the data needed for a decision on stroke classification, but will have no knowledge of the patient's medication history.

4. Criteria for Control Selection

Control subjects (two per case) will be individuals who satisfy overall study eligibility criteria and who meet specific criteria for control selection. Controls will be chosen as a representative sample of the population by random digit-dialing. Controls will be individually matched to cases for age (within 3 years for those less than 30, and within 5 years for those 30-49), for gender (male, female), for race (white, non-white), and for telephone exchange. (For further control of social class, analytic adjustment will be made for any inequalities in education.)

A further requirement of the selection process is that controls be identified and enrolled within 14 days of the matched case's stroke event. This requirement ensures that controls and cases are concurrent by calendar time and chosen from the same season of the year.

5. Specification of Zero-Time and the Exposure Window

Zero-time refers to a period in the patient's history before the index event (stroke in cases and corresponding date for controls) during which clinical features are assessed and exposure to risk factors is determined. The most appropriate zero-time is a period in which the patient's clinical state could elicit medication use (e.g. cough or cold symptoms), and for which the exposure could lead subsequently to the suspected outcome.

The definition of phenylpropanolamine use and the choice of an exposure window depends upon the analysis for each specific aim. To answer the first and third specific aims, we shall examine all use of phenylpropanolamine. The second aim requires that phenylpropanolamine exposure be classified separately by its nonprescription indications for use.

This simple principle of tailoring the exposure definition to the specific aim also applies to the timing of phenylpropanolamine use. The analysis for the first and second specific aims will be based on a three-day exposure window, while the analysis for the third specific aim depends only on first dose/first day exposure. Under this first dose/first day specification, a patient would be counted as "exposed" only if the index event (stroke in cases or corresponding date in the controls) occurred within 24 hours of the first dose of phenylpropanolamine used by the patient. Patients are counted as "non-exposed" whenever the first dose occurred more than 24 hours before the index event (regardless of continued use of phenylpropanolamine).

We intend to be flexible in secondary definitions of exposure by examining the use of phenylpropanolamine products. We also intend to conduct a series of additional analyses to explore the impact of dose and timing of use on the association between phenylpropanolamine and hemorrhagic stroke. In these planned analyses, we shall look at the influence of recency (time from last use) and latency (time from first use) on the association between phenylpropanolamine use and hemorrhagic stroke.

6. Stratification by Indication for Use

The indication for use of phenylpropanolamine-containing products may be an important consideration in the assessment of any risk for hemorrhagic stroke. The two main indications for non-prescription phenylpropanolamine use are for relief of cold and cough symptoms and as an appetite suppressant.

Neither cough/cold symptoms nor appetite suppression are major potential sources of susceptibility bias (confounders). Since neither indication is a known prognostic factor for hemorrhagic stroke, we expect

that cases and controls will contain equal proportions of individuals with these indications at zero-time. Nevertheless, we do wish to examine whether the indication for use could modify any effect observed in the relationship between phenylpropanolamine containing products and hemorrhagic stroke. Consequently, we plan to conduct overall analyses for all subjects in the study, and then according to strata defined by indication-for-use.

7. Type of PPA Use

An additional feature of exposure in this study concerns the type of product in which phenylpropanolamine is contained. For instance, it is possible (although we suspect unlikely) that phenylpropanolamine in appetite suppressants confers a different risk than phenylpropanolamine in cough/cold remedies. This difference in type of phenylpropanolamine is distinct from the separate issue of indication for use noted earlier. The latter examines a characteristic of patients while the former considers the characteristic of the product.

To address the possible differences in association by type of phenylpropanolamine, we plan to conduct analyses in which the specific type of phenylpropanolamine product is the exposure variable.

8. Measures of Susceptibility Features (Confounders)

The relationship of drug use to an adverse outcome generally, and phenylpropanolamine use and hemorrhagic stroke specifically, may be biased if the compared groups were substantially unequal in their initial susceptibility to the outcome (13). For example, if diabetics are both more likely to use appetite suppressants and are at greater risk for hemorrhagic stroke, an association between appetite suppressants and hemorrhagic stroke may result from "susceptibility bias", rather than a pharmacologic effect of the appetite suppressants. Comparable concerns

can be raised regarding the analysis of cough and cold preparations. For instance, smokers may be more likely to use cough/cold products and to have an increased risk of stroke. To overcome this potential source of bias requires the collection of suitable data on features associated with an increased risk of stroke, including indications for phenylpropanolamine use, and appropriate adjustment in the analysis.

The following features, which are possible sources of susceptibility bias, can be grouped under two headings: (a) sociodemographic; and (b) patient characteristics;

a) Sociodemographic Features:
(Each of these features is included as a matching factor.)
- age
- gender
- socioeconomic status (using telephone exchange)
- race

b) Patient Characteristics
- hypertension
- obesity (height/weight ratios)
- diabetes
- smoking
- other medications
- Kaplan-Feinstein Comorbidity Index
- alcohol use
- illicit drugs, including cocaine
- family history of hemorrhage

9. Data Collection

The data will be collected by researchers (data technicians) employed for the purpose of conducting this research. All data technicians will have a complete understanding of the research methodology and will be trained in the conduct of field procedures and

standardized methods of interviewing and data collection. Physician-researchers will review the clinical data and will be responsible for decisions in which clinical judgment is necessary; all other decisions regarding data collection and quality will be the responsibility of the project epidemiologist (CMV).

The purpose of each data collection form and the way in which each will be used are summarized briefly in the sections that follow. To date we have prepared drafts of two data collection forms. We have not yet prepared the in-depth interview form.

a) Case Identification Form

Whenever a potential case is identified by the surveillance team, a researcher will complete a Case Identification Form. This form will include data that will enable the researchers to decide whether the patient satisfies case eligibility criteria (i.e., clinical presentation, selected physical examination findings, brain imaging studies, etc.). Identifying data (other than the subject code number) will be added to the form only after verbal consent for participation has been provided.

As noted previously, if a patient is thought not to satisfy eligibility criteria, the Case Identification Form for that patient will be retained for review by the panel of experts to confirm that the researchers' decision to exclude the patient was appropriate.

b) Control Screener Form

Information collected on the Case Identification Form will include data that enable the selection and matching of control subjects. Using these data, a screening interview by telephone of potential controls will be conducted to determine whether the subject satisfies eligibility and matching criteria. All information from the screener interviews will be recorded on a Potential Controls Form and will be available for later review.

c) In-Depth Interview

The researchers will conduct an in-depth interview with all cases and controls. The interview data form contains a detailed history of the patient's history, the index illness, known or suspected stroke risk factors, medication history, and indications for use of diet aids or cough/cold preparations. The following precautions will be taken to ensure the quality of data and to prevent the introduction of bias.

1) Use of Direct Interviews

All subjects will have in-depth interviews conducted face-to-face, unless a telephone interview is requested. In this way, we hope to equalize the context in which the interview is conducted, and the impact of the questioner on the interview process. The site of the interviews for cases will be variable, and may occur either in the hospital, a nursing home or rehabilitation center, or at the patient's home. For controls, most interviews will be conducted at the patient's home, although some control patients may be living in nursing or rehabilitation facilities.

2) Timing of Interviews

To ensure high quality data and enhance accurate recall, we plan to interview cases as soon after enrollment as possible. This plan will minimize the time from the stroke event to the interview date. Cases and controls will be asked to recall exposures occurring at the same distance in time. For instance, if a case is interviewed 1 week after her stroke about the 3 days preceding that event, the control would also be asked to recall a 3 day interval 1 week ago. Although this strategy creates a somewhat arbitrary landmark for controls, it ensures that both cases and controls are required to remember over a similar length of time.

3) Confirmation of Medications

All information on prescription and non-prescription medications will be obtained first by interview questions. To assist identification of medications, product identification charts will be shown to subjects (the use of these charts will be noted for each identification). Only after these oral responses are concluded will subjects be asked to confirm their use of medications by showing drug containers to us.

If subjects are not interviewed at home, they will report medications to us in an identical manner, including the use of product identification charts. After providing this information, they will also be asked to provide additional confirmation of medications using the following strategies (in order of preference).

a) Someone will bring the medication from home. This might include a researcher going to the home to pick up the medication.

b) The interviewer will speak to someone by telephone to obtain details of the medications in the house (including lot numbers, when available).

c) On occasion, labels or the copied details of labels may be requested to be sent by mail.

Definite exposure to a medication will require both verbal identification and either picture identification or production of a bottle or container. This strategy will ensure a high degree of precision in the identification of subjects as exposed or non-exposed to specific medications.

4) Additional Measures to Standardize Data Collection

All interviewers, who will be blind to the study hypothesis, will be trained in standardized methods of obtaining data.. Periodically, interviewers will be observed conducting interviews, both by telephone

and face-to-face. Errors or inconsistencies in the interview process will be noted and corrected. Persons conducting each interview will be interchangeable and randomly assigned to cases or controls to further ensure that no systematic bias is introduced in data collection.

5) Reasons to Avoid Surrogate Interviews

When the FDA initially proposed limiting the cases and controls to subjects who were alive at the time of the interview, the investigators dissented because of concern that selection bias might distort the measured association between phenylpropanolamine use and hemorrhagic stroke. At that time, we suspected that the effects of misclassification bias were less worrisome than the effects of selection bias. Modeling the effects of misclassification bias convinced us otherwise — that the cases and controls should be limited to living subjects. The following illustrates the basis for our position.

Assume that the true odds ratio between phenylpropanolamine and hemorrhagic stroke is 3.0: that the true exposure prevalence in controls is 0.502% and in cases is 1.492% (these exposure prevalences will be used for the first-dose analysis in planning sample size). Assume that 30% of the cases are dead or impaired, requiring surrogate interviews for these cases and their matched controls. Assume also that surrogate interviews have a sensitivity of 50% and a specificity of 90%. In the final analysis, the study will be comprised of two strata, one with direct interviews of living subjects, the second with interviews of proxy subjects. The direct stratum will yield a measured odds ratio of 3.0, which faithfully reflects the true odds ratio. However, the proxy stratum has a measured odds ratio of 1.04 that misrepresents the true value of the odds ratio. When the strata are combined, the measured odds ratio is 1.25. These two subgroups defined by distinctive sources of

data are highly heterogeneous, yield different estimates of the odds ratio, and are non-combinable on the basis of methodologic and statistical principles. For that reason, we now believe that only living subjects should be included in the main analyses for this study, accepting the theoretical possibility for some selection bias.

The quantitative evidence for the unexpectedly large impact of misclassification bias is presented in the following table. This table displays the effects of the bias on a range of true odds ratios varying from values of 3.0 to 6.0. The measured odds ratio for the direct interview stratum are identical to the true values, since we assume that direct interviews have perfect sensitivity and specificity. The measured odds ratios for the proxy or surrogate interview stratum assume a sensitivity of 50% and specificity of 90%. The final odds ratio for the combined strata is based on using proxy interviews for 30% of cases and controls. In all instances, misclassification bias leads to severe attenuation of the combined measured odds ratios (from 1.25 to 1.62).

EFFECT OF 30% PROXY RESPONDENTS
ON MEASURED ODDS RATIO*

True Odds Ratio	Direct Interviews Stratum	Surrogate Interview Stratum	Combined Strata Odds Ratios
3.0	3.0	1.04	1.25
3.5	3.5	1.05	1.31
4.0	4.0	1.06	1.37
4.5	4.5	1.08	1.43
5.0	5.0	1.09	1.50
5.5	5.5	1.10	1.56
6.0	6.0	1.11	1.62

*Sensitivity of proxy respondents = 50%
Specificity of proxy respondents = 90%
Control exposure = .502%

10. Consent Procedures

The consent procedures used in this study have been reviewed and approved by the Yale University Human Investigation Committee. Further

approval will be sought from all hospitals enrolled in the Active Surveillance system. Approval to speak to a case will be obtained from the attending physician responsible for the patient's care.

11. Procedures to Ensure the Confidentiality of Study Participants

All data abstraction forms, photocopies of charts, and computerized data will be kept by the researchers at Yale University School of Medicine. However, we recognize that this study may generate requests for review of data by regulatory agencies, sponsoring companies, and other investigators. Consequently, we shall undertake the following precautions:

a) The "front page" of the data collection forms and the consent forms will contain all the necessary identifying information and will be filed separately from all other data. These will not be released to external reviewers.

b) All other data collection forms and photocopies of medical records will be identified by a code identification number only.

c) Subjects will be notified that some information may be reviewed by persons other than the researchers. Subjects will be informed of the provisions taken to ensure that they will not be identified.

12. Data Management and Analysis

The data obtained from hospital records and patient interviews will be transferred onto specially prepared coding forms. The data will then be entered directly on file for computer analysis.

In the first phase of the analysis, we shall compare cases and controls for similarity on variables considered crucial to the study's validity, including the features noted in the section on susceptibility bias. Any differences noted in this phase of the analysis can be adjusted in the final analyses to avoid confounding.

The second phase of the analysis will estimate crude or "unadjusted" odds ratios for the association between phenylpropanolamine use and hemorrhagic stroke. Although unadjusted for susceptibility features, the analyses will incorporate the matched design that contributes to the study's validity. Adjusted odds ratios will reflect the best estimates of the association between phenylpropanolamine use and hemorrhagic stroke, after controlling for features distributed unequally between the cases and controls.

A further analysis, in which we shall stratify the data by severity of the stroke, may assist in estimating the effects of selection bias. In this analysis, more severely affected cases and their controls will be analyzed separately from cases with mild-moderate strokes. Variation in the size of the association between PPA and hemorrhagic stroke would suggest the possibility of selection bias.

Stochastic significance of the odds ratio will be measured with the chi-square test. Confidence intervals around the odds ratio will be estimated using standard methods (14). Where applicable, the Mantel-Haenszel or other analytic procedures will be used to examine the results across several strata, and to estimate summarized chi-square values. In addition, as noted earlier we plan to conduct suitable multivariable analyses to adjust for the effects of potential susceptibility variables ("confounders").

13. Sample Size Estimation

In calculating the sample size, we needed to obtain the best available estimate for phenylpropanolamine use in the control population. We used the MRI market research data to estimate the proportion of subjects in the population who were using phenylpropanolamine products. The MRI conducts a national survey, and

data are available on the New England Region generally, and the states of Connecticut and Rhode Island together. Furthermore, data are assembled separately for diet pills and cough/cold products. We restricted the survey data to the recent years 1990, 1991, and 1992, to take account of changes in product availability. During this interval, all of the diet pills available contained phenylpropanolamine; based on the top 27 brands of cold and sinus products and top 12 brands of cough syrups, we estimate that 30% of sales of cough/cold products contain phenylpropanolamine.

Because the Connecticut/Rhode Island survey conducted by MRI was based on approximately 500 subjects in each year (1990, 535; 1991, 466; 1992, 448), we repeated the calculations using the larger unweighted sample for New England (approximately 1500 subjects each year). Since our calculations were similar when we used the New England region and Connecticut/Rhode Island alone, we believe the estimations we present are accurate and representative of phenylpropanolamine users.

The most extreme set of assumptions for calculating sample size arises from the need to estimate the risk of hemorrhagic stroke associated with the first dose/first day use in women 18-49 years of age. For that reason, we shall begin by calculating the sample size needed to detect this first dose effect and then examine the study's power to detect clinically important increases in the odds ratio for the other study aims.

a) First Dose/First Day Effect

In calculating the sample size, we employed a series of assumptions. First, we restricted the subjects to women ages 18-49. Second, we used any type of phenylpropanolamine (Cough/cold or appetite suppressant). Third, we set the desired odds ratio to detect at a value of 5.0. Fourth, we set $\alpha = .05$ and $\beta = .20$. Finally we used a one-tailed test of significance.

Using data from the MRI survey of Connecticut and Rhode Island referred to earlier, we can estimate the proportion of subjects who used phenylpropanolamine in the last 30 days. Since we are interested only in the first use each month, we divided the proportion of users by 30 to estimate the proportion of first dose users. For appetite suppressants, during the period 1990-1992 the average proportion of users in the last 30 days was 1.6%, yielding an estimate of first-dose users of 0.05%. The estimates for cold and cough preparations were 0.92% and 0.58%, respectively. We used the conservative estimate of 30% to calculate the proportion of cough/cold users with phenylpropanolamine-containing products (based on sales figure), to yield values of 0.28% and 0.17%, respectively. Thus the estimated overall first dose exposure in controls is 0.502%.

The sample sizes required for a one-tailed test (α = .05), at odds ratios from 4 to 6, and with beta error varied from .1 (90% power) to .3 (70% power) are displayed below. For the one-tailed test with 80% power to detect an odds ratio of 5.0, for the association of first dose phenylpropanolamine to stroke, 324 women ages 18-49 are required (assuming two controls per case). At 80% power, the required sample size ranges from 240 to detect an odds ratio of 6.0 to 483 to detect an odds ratio of 4.0.

NUMBER OF REQUIRED CASES* BY ODDS RATIO AND POWER OF TEST
(ALPHA = .05, 1-TAILED)

	Odds Ratio				
Power	4.0	4.5	5.0	5.5	6.0
70%	360	289	240	205	178
75%	412	331	275	235	204
80%	483	389	324	276	240
85%	572	461	384	328	286
90%	696	562	469	401	349

*Assumes 2 controls per case

Accepting the one-tailed test at a significance level of .05 and assuming 350 cases and 700 controls comprised of women ages 18-49, the study has the following power: 95% to detect an odds ratio of 6.0; 90% for an odds ratio of 5.5; 83% for an odds ratio of 5.0; 74% for an odds ratio of 4.5; and 63% for an odds ratio of 4.0. For all of these calculations, the estimated sample size refers to subjects alive and able to communicate at the time of the interview (no surrogate interviews).

b. Any Phenylpropanolamine Use

This analysis includes men and women ages 18-49, using phenylpropanolamine in appetite suppressants or cough/cold products. In this analysis, exposure is defined as three days before the index event. To calculate an expected control exposure for this time period, we used data from the MRI survey on the mean number of uses among users in the past month (13 for diet pills, 9 for cold medicine, and 5 for cough remedies). Using these data, and assuming complete dependence across days of use among users in the past month, we estimate a control exposure rate over any 3 day period for any phenylpropanolamine use of 4.52%. Assuming this exposure rate, a study with equal numbers of men and women with hemorrhagic stroke (i.e., 700 total alive cases and 1400 alive controls) would have exceedingly high power to detect clinically meaningful odds ratios as follows: 98% for an odds ratio of 2.0; and 99% for an odds ratio of 2.5.

c. Phenylpropanolamine Use by Indication

For the association between phenylpropanolamine used in cough/cold preparations and the risk of hemorrhagic stroke, all subjects are included in the analysis. We estimate an exposure control rate (for 3-day window) of 3.90% (for ages 18-49), leading to the following level of statistical power: 96% for an odds ratio of 2.0; 99% for an odds ratio of 2.5.

For the association between phenylpropanolamine in appetite suppressants and the risk of hemorrhagic stroke, only women age 18-49 are included in the analysis. Assuming an exposure control rate (for 3-day window) of 0.64% results in the following levels of statistical power: 36% for an odds ratio of 2.0; 79% for an odds ratio of 3.0; 98% for an odds ratio of 4.0.

d. Monitoring Control Exposure

We recognize that the control exposure rates used to calculate the required sample sizes are based on survey estimates. To ensure that the study is suitably sized for our objectives, we propose to monitor the control exposure rate after 100 and 200 controls are enrolled. No attempt will be made at this point to conduct any analyses of effect size or statistical significance. The purpose of the monitoring is only to inform us whether sample size planning was based on sound estimates of phenylpropanolamine use among control subjects.

14. Interim Analysis

We propose one interim analysis, conducted after half of the sample has been enrolled (350 men and women cases including at least 175 women, 700 men and women controls). The interim analysis will focus on the first (any phenylpropanolamine use, 3-day window, men and women) and third (appetite suppressant phenylpropanolamine use, first day/dose window, women only) objectives. To preserve the specified sample sizes, we intend to use the O'Brien-Fleming methods for testing the significance of effect estimates. The O'Brien-Fleming significance level is 0.005 for the first look and 0.048 for the second and final look. As you know, the O'Brien-Fleming boundary is not a decision rule but rather an indication that further evaluation of early stopping is needed. The rule ensures that, if early termination is not done, the final look will be at the .05 significance level.

15. Availability of Cases

Cases will be recruited from four sites: Connecticut; Providence, Rhode Island; Cincinnati, Ohio; and Houston, Texas. Each site assembled estimates of cases of hemorrhagic stroke (ICD 430-432) for men and women ages 18-49. A summary of these estimates (for a 12 month period) is as follows:

Diagnosis	Connecticut	Providence, Rhode Island	Cincinnati, Ohio	Houston, Texas
• Men (18-49)				
430 subarachnoid hemorrhage	31	10	17	(data pending)
431 intracerebral hemorrhage	30	13	8	
432 other hemorrhage	10	5	0	
	71	28	25	
Diagnosis				
• Women (18-49)				
430 subarachnoid hemorrhage	41	14	17	(data pending)
431 intracerebral hemorrhage	11	8	12	
432 other hemorrhage	2	1	0	
	54	23	29	

Thus, we anticipate a pool of potential cases (excluding Houston, Texas) equal to 230 subjects per year among the four sites. Over our enrollment period of 42 months, we can expect 805 subjects (excluding Houston) to ensure that we meet our sample size requirements.

16. Early Termination (or Modification) of Study

Consistent with sound scientific management, we have identified explicit reasons for early termination or modification of the study. All decisions to terminate the project early would require consultation among the study sponsors, investigators, and scientific advisory group.

a) Early termination or modification will occur if, after the first 12 months, the study fails to achieve 50% of its anticipated goals

for case recruitment. Close continuous monitoring monthly is intended to avoid this problem.

b) Evidence for poor data quality that impairs the validity of the research (e.g., high refusal rates, large amount of missing data in interviews, etc.)

c) Interim analysis reveals elevated risk between phenylpropanolamine and hemorrhagic stroke that is statistically significant.

d) Failure to adhere to standard financial practices and methods of accountability.

E. Scientific Advisory Group

The Scientific Advisory Group (SAG) for the Hemorrhagic Stroke Study will serve as a general oversight committee for the project. The SAG will have several distinct functions: (1) to review the protocol and to suggest modifications; (2) to review and monitor the progress of the study; (3) in consultation with the Hemorrhagic Stroke Study investigators to develop criteria for deciding whether to terminate the study prematurely; and (4) during the course of the study, to relate to the sponsoring companies and their scientific committees.

We consider the scientific autonomy of the SAG from both the investigators and the sponsors to be paramount. Consequently, we expect that the SAG will be constituted and will function according to the following guidelines:

1. That the SAG will be free to conduct its meetings, maintain its records, and interact with the investigators and the scientific community in whatever manner they deem appropriate;

2. That the SAG will be free to make public its opinions concerning the study not later than 60 days after the study results have been made public.

Financial support for the SAG, including travel, honoraria, and administrative costs, will be furnished by the investigators. The SAG will maintain strict financial accountability. However, this financial accountability will not imply accountability to the Yale researchers or to the sponsors for the scientific decisions of the SAG.

F. Administrative and Field Operations

1. Administrative

Dr. Ralph I. Horwitz, as Principal Investigator, assumes overall responsibility for the scientific activities of this project. He is joined in these duties by Dr. Lawrence M. Brass, Co-Principal Investigator and Chief Study Neurologist, who will also be responsible for all aspects related to the network of participating neurologists in Connecticut. Dr. Catherine M. Viscoli, as head epidemiologist, will be in charge of data forms and data management and will advise on issues of design and analysis. Dr. Walter N. Kernan is the co-investigator responsible for field activities and will work closely with the Field Director (TBN) who will be responsible for the overall management of the study staff and its field activities.

All reports to the Sponsor on the financial aspects of this project will be the responsibility of Dr. Horwitz. Dr. William Soller will serve as the main liaison between the sponsoring companies and the investigators. Ms. Elizabeth Pesapane, Project Administrator, will monitor the distribution of funds and prepare periodic financial reports as well as ensure that all sites are in compliance with HIC requirements, that administrative and financial procedures are followed, and that communication across sites is achieved. Ms. Chris Van Vranken, Administrative Assistant, will be responsible for all of the clerical and technical support for the project.

2. Field Operations

There are three main components to the field operations of the Hemorrhagic Stroke Study: (1) establishment and maintenance of surveillance network; (2) identification and enrollment of cases and controls; (3) in-depth interviews of enrolled subjects. The surveillance, which has been described earlier in the protocol, will be directed by Dr. Brass in cooperation with the Yale Field Director (TBN). A vascular neurologist (TBN) will review all incoming data related to the intracranial hemorrhages for patients recruited into this study. The vascular neurologist will be responsible for working with the Field Director to obtain any missing clinical data necessary for the neurological evaluation of the individual patients in this study. Identification and recruitment of study subjects (cases and controls) will be the responsibility of Dr. Kernan working closely with the Field Director. All aspects of subject interviews and data collection will be supervised by Dr. Viscoli in cooperation with the head data technician. Three interviewers (TBN) will be responsible for enrolling cases and controls at the Yale site, and will conduct the interviews (screening and in-depth) that are integral to the data collection process.

3. Sequence of Activities

a) Field Director will be hired as soon as possible after funding of the project;

b) Establish the coordination of Connecticut surveillance network, and networks in each of the affiliated sites, including approval of protocol by each of the hospitals and selection of each hospital's surveillance officer;

c) Establish similar networks in Providence, Rhode Island; Cincinnati, Ohio; and Houston, Texas.

d) Develop in-depth interview and begin field-testing all procedures and instruments;

e) Hire and train data technicians;

f) Begin enrollment and interview of cases and controls.

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