DESCRIPTION OF A PHARMACY BASED INVESTIGATIONAL DRUG CENTER AT A UNIVERSITY TEACHING HOSPITAL

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Preface

The University of Wisconsin Hospitals at Madison is a 600 bed teaching facility with a full compliment of medical services including a 100 bed pediatric hospital, 100 bed oncology center, 35 bed psychiatric unit and a 10 bed trauma and life support center. The medical staff is active in drug research.

The pharmacy department uses a computer assisted centralized unit dose drug distribution system with decentralized pharmacists. The department provides twenty-four hour service, a hospital wide I.V. admixture program, an extemporaneous bulk and sterile manufacturing service and a centralized drug information center. Pharmacy technicians are responsible for the administration of medications on six of the hospital patient care units.

In order to assist investigators with drug control procedures, the pharmacy department developed a system for coordinating drug activities associated with research. The information, considerations and process involved with the development of a pharmacy based investigational drug center, as experienced by pharmacist David Zilz, Thomas Thielke, and the author of this paper, are related in the text which follows.

Introduction

The Federal Food and Drug Administration (FDA) and hospital pharmacists share a common goal - getting the best drugs possible to patients. The FDA regulatory system for drug products is a lengthy and tedious process aimed at protecting the public from nonefficacious and unsafe drug entities (Appendix A). It evolved in response to incidents such as the sulfanilamide elixir tragedy of 1937 and the European thalidomide disaster of 1961, when thousands of people were injured because of inadequate trials with these agents.[1] Investigators criticize the lengthy process required to obtain marketing approval for new drugs, and accuse the FDA of keeping drugs that have been proven effective from the American public.[2] Nevertheless the FDA requires substantial evidence of the safety as well as effectiveness of new drugs.The increasing percentage of new products developed outside the United States is used by critics to support their accusations.[3]

A new drug must complete successfully several stages of study and the regulatory requirements of the New Drug Regulations promulgated under the Federal Food, Drug and Cosmetic Act (FD & C Act), section 505, as amended in 1962.[4] Initially, a chemical substance is tested in the laboratory on animals for pharmacologic activity, toxicity, and to determine general therapeutic dosages. If a chemical shows promise as a useful therapeutic agent, the sponsor submits a Notice of Claimed Exemption for a New Drug (IND) to the FDA

1. Kaluzny, E.L., Pharmacy Law Digest, Douglas-McKay Inc.,Milwaukee,Wi., 1973, pg. 166.14-166.17.

2. Fries, E.D., "The Drug Lag", JAMA, 235 No.5,475,1976.

3. " Policy on Clinical Research", Pharmaceutical Manufacturers Association, Washington, D.C., unpublished, July 1975.

4. 21 CFR 310, 312 & 314.

indicating an intention to test the drug in humans. The data submitted provide the FDA with information about the composition of the drug, if known, its source, and how it was made. Submitted along with the IND are the results of all animal studies and a detailed protocol describing the planned testing in humans. The FDA has thirty days in which to review the application for evidence of unwarranted risks to patients and to inform the sponsor of any complications prohibiting the initiation of the study.

After the thirty days, the sponsor may initiate human testing of the chemical, which is now considered an investigational drug. Clinical investigators, qualified to engage in human research, are contacted to participate in the evaluation of the investigational drug. Before a drug can be tested on institutionalized subjects, the protocol must be reviewed by an Institutional Review Committee (IRC) consisting of representatives of various disciplines such as physicians, clergymen, social workers, lay persons, and lawyers to help assure patient rights are adequately protected.[5]

Ther are four phases of investigational drug testing in humans required by the FDA. "The first phase of human testing is directed at determining what chemical actions a drug has, how it is absorbed into the body, how it should be given, and what the safe dosage range is."[6] These tests use a small number of volunteer subjects and, based on information from the FDA, have an excellent safety record.[7] Once Phase I studies adequately prove the chemical does act in the body and is safe, Phase II studies can be initiated.

5. 21 CFR 312.1

6. Pines, W.L.,"A Primer on New Drug Development", FDA Consumer,Feb 1974, pg.1.

7. ibid.

Phase II studies evaluate the effectiveness of a drug on a limited number of patients with a specific disease, or its effectiveness at prophylaxis against a disease. The number of patients in which tests are performed depends on the nature of the drug and the disease state.

Phase III studies, the most extensive testing phase of a new drug, are intended to "assess the drugs safety, effectiveness and most desirable dosage in treating a specific disease...".[8] The drug is used on a large number of patients and is administered by the route and in the dosage range in which the marketed product would be.

All phases of human testing must be conducted as well controlled investigations. The investigator must be able to determine that changes in subjects are related to the administration of the drug, and not to other variables. These types of studies produce "substantial evidence"[9] of a drug's safety and efficacy which is required for New Drug Applications (NDAs) to the FDA.

A NDA contains the production and preclinical information the sponsor has about a drug.[10] Applications are made to one of six divisions of the FDA responsible for reviewing, evaluating and approving NDAs for certain categories of drugs.[11] If safety and efficacy are adequately demonstrated, the FDA may approve the application and the drug can be marketed. After approval is granted, monitoring of the drug continues to appraise its continued safety and efficacy. This is considered Phase IV of the required human testing.

Phases I,II, III and IV are required for all drug products, but the FDA may require additional studies to evaluate the long term effects of a drug

8. Pines, W.L., op. cit., pg. 2.

9. 21 CFR 314.11.

10. 21 CFR 314.

11. Pines, W.L., op. cit., pg. 3.

on a large number of patients. These studies, performed under conditional NDA approval, make the drug available for use, but require that the drug sponsor continue well controlled animal and clinical studies to complete the information base on the safety and efficacy of the drug.

Most clinical drug research is performed on institutionalized subjects.[12] Hospitals and other patient care institutions are responsible for safeguarding the rights of their patients and must make a concerted effort to regulate and coordinate investigational drug use within the institution. Professional organizations and governmental agencies are requiring or recommending increased hospital responsibility for the development of policies and procedures integrating the clinical monitoring, distributive and organizational aspects of investigational drug studies performed within the institution. Unfortunately, standard policies and procedures have not been developed and tested to support a coordinated, flexible, hospital-wide investigational drug system.

Hospital pharmacists, because of their common goal with the FDA of getting the best drugs possible to patients, should take the initiative for developing a set of policies and procedures for a coordinated hospital system concerned with the control of investigational drugs. The primary responsibility of hospital pharmacists is the coordination of all aspects of medication use within the institution. This is accomplished through developing and implementing a restricted formulary, providing accurate medication control through maintenance of a medication distribution system, and providing clinical services. Many hospital pharmacists provide these services for noninvestigational drug

12. Arbit, H.M.,"Regulatory Aspects of Investigational New Drugs", Presented at ASHP Midyear Clinical Meeting, Anaheim, Cal. Dec. 1976.

products only, but The American Hospital Association, The American Nurses' Association and The American Society of Hospital Pharmacists recommend that pharmacists take an active role in coordination of investigational drug use within the institution. Principle number five in "The Statement of Principles involved in the use of Investigational Drugs in hospitals" states:

> "The pharmacy department is the appropriate area for the storage of investigational drugs, as it is for all drugs. This will also provide for the proper labeling and dispensing in accord with the investigator's written orders."[13]

Pharmacists are experienced with inventory control and storage of drug products, and can apply this knowledge to investigational drugs. They can provide a controlled distribution system for the investigational drugs and information about their use. Because of the pharmacist's drug control expertise, hospital pharmacists could provide the type of coordination required for a hospital investigational drug program.

Problem

Traditionally, investigational drug control and coordination have been the responsibility of individual investigators or medical departments in cooperation with the pharmaceutical manufacturer sponsoring the drug study. Study protocol development, drug distribution, drug information dissemination and study data collection were performed by individual investigators using various methods. There were limited hospital policies or procedures providing guidance for the systematic use of investigational drugs.

13. "Statement of Principles involved in the use of Investigational Drugs in hospitals", ASHP, Am. J. Hosp. Pharm., 19,509, 1962.

Personnel, involved with investigational drug studies in a hospital with no coordinated investigational drug control program, encounter problems related to the lack of knowledge about the requirements of clinical research. Generally, physicians are not trained or experienced with investigational drug procedures and therefore experience problems with clinical research that may be avoided. Typical statements made by physician-investigators, to members of the pharmacy department at University of Wisconsin Hospitals-Madison, about problems they encountered with investigational drug procedures referred to:

1) The ambiguity of legal requirements for clinical research,
2) The number of regulations and the lengthy paperwork to be filed before FDA approval for a study is granted,
3) Delays in study initiation due to the required federal and hospital committee reviews, and
4) Lack of a capable person to coordinate the paperwork and coding for blinded studies.[14]

Nursing and pharmacy personnel experienced significant problems in the distribution and administration of investigational drugs. Supplies of investigational drugs were not always available when investigators were away from the institution. Labeling of drug supplies was often inadequate, and information about side effects and administration techniques was not accessible.

The Institutional Review Committee of the Center for Health Sciences, responsible for the initial approval and continuous monitoring of research studies for the hospital, must judge the acceptability of drug studies in

14. Vinti, R.A.,"Survey conducted at UWH - Madison,"unpublished, Feb. 1976.

terms of institutional regulations, relevant laws and standards of professional practice.[15] Often the IRC does not have nor can readily obtain the necessary expertise to evaluate drug related information.[16]

Hospital administration was concerned that the current investigational drug "system" provided inadequate coordination and placed the institution in a precarious medical-legal situation.[17] The illegal transfer of study drugs to affiliated hospitals where study protocols had not been reviewed was another problem.

Administration of investigational drug studies has posed a problem for the pharmaceutical manufacturer.[18] Companies spend considerable amounts of time, effort and money recruiting investigators to conduct drug studies in individual institutions. Often the selected investigators lack adequate funds and personnel to provide storage and dispensing methods conforming to product or legal requirements. Records often are kept inadequately and patient monitoring limited to the investigator alone. This may produce inaccurate reporting of study data to the company. Non-conformity to company study protocol produces questionable study results. Inadequate monitoring capabilities from within the institution increases the sponsor's burden of monitoring clinical research protocol conformity.

To some extent these problems are common to all investigators, hospitals and pharmaceutical manufacturers. Therefore, ther is a need for a local coordinating body for investigational drug activities, such as a comprehensive pharmacy based investigational drug center. Implementation of this program

15. 21 CFR 312.1

16. Vinti, R.A.,op. cit.

17. ibid.

18. ibid.

alleviates many of the problems associated with investigational drug use within a hospital while creating a hospital expertise in this field.

Considerations

The development of such a program requires a thorough knowledge of the current status of investigational drug research in the hospital. Procedures currently used for approving and monitoring clinical research should be reviewed to determine areas requiring modification. Information about the number of drug studies currently being performed and the number expected in the future provides a general insight into the extent of clinical research within the hospital and the amount of effort a pharmacy based program would entail. Both federal and hospital requirements for clinical research should be reflected in the type of program developed by the pharmacy department and the institution.

An essential aspect of any hospital based investigational drug program is hospital committee involvement in the investigational drug approval and monitoring procedures. Usually the IRC operates as a hospital committee, but the Committee for the Protection of Human Subjects (CPHS), University Hospitals' IRC, is a Center for Health Sciences' Committee, and is responsible for reviewing human research proposals for the Medical, Pharmacy, Nursing schools, and the school for Allied Health Professions as well as the hospital. This necessitated the development of a liaison between a hospital committee and the CPHS in order to obtain the necessary hospital involvement in research review. The Pharmacy and Therapeutics (P&T) Committee, an advisory group to the medical staff, is responsible for developing and recommending policies on the use of drugs in the hospital. Because of its mandate and generally

accepted pharmacy membership, it is a logical committee to coordinate hospital policies on investigational drug procedures. Joint membership of two members of the P & T Committee, a pharmacist and a physician, on the CPHS provides the necessary communication to permit hospital involvement in the research approval process. This liaison between the two committees also makes any expertise existing on the P & T Committee accessible to the CPHS.

Another important component of the program is pharmacy department involvement early in the investigational drug process. This enables pharmacists to provide guidance to investigators on protocol development and proper application procedures for hospital and federal study approval, while keeping the department informed of new studies proposed for performance in the hospital. Several mechanisms were available through which early involvement could have been obtained. Mandatory P & T Committee review of all clinical research proposed for performance at the hospital is one method. The medical and pharmacy personnel, through membership on the committee, learn about research before it is initiated and can make recommendations to investigators should potential problems exist. The difficulty with this type of procedure is duplication of the activities of the CPHS which would complicate and lengthen the hospital approval process.

Another method relies on investigator initiative to contact the pharmacy department. This would alleviate the additional committee review, but is not a reliable method for keeping informed of new research. Usually, investigators do not contact the pharmacy early enough in the process, if they approach the department at all.

Pharmacist membership on the CPHS, consistent with the P & T - CPHS liaison, allows pharmacy involvement in the process before hospital approval

is granted without burdening the approval process with another committee review. Along with membership on the committee, the pharmacy department should become the hospital's source of documents required for application to federal and hospital approval agencies. Investigators, seeking assistance in the application process, then can utilize the pharmacy as an information resource.

The establishment of minimum standards for study design and investigational drug control is essential to any program affecting institutional use of study drugs. These create a minimum level of practice which all research must meet or exceed. IRCs, concerned with the human aspects of clinical research, develop guidelines for study design and make them available to prospective investigators; but control guidelines for investigational drugs generally have not been available to individual investigators. Development of these standards is the responsibility of the drug control experts in the hospital, the hospital pharmacists. Acceptance of these standards by the P & T Committee, IRC and hospital governing board is necessary if they are to apply to all clinical research performed in the hospital. Like the guidelines for study design, the drug control requirements direct investigators toward the performance of clinical research which conforms to federal and hospital regulations.

Enforcement capability is a necessary component of any effective program. It is imperative that the enforcement be administered by an appropriate agency; one having the type of relationship to, and authority over, investigators to effectuate this aspect of the program. The IRC, a logical choice in other institutions because of its authority to grant, deny and revoke hospital approval for research, was not a suitable alternative in University Hospitals.

The CPHS, a Center for Health Sciences committee, is physically remote to the hospital and enforcement of hospital policies is not a part of their jurisdiction. The membership maintains a part-time commitment to the committee and therefore cannot provide adequate monitoring capabilities required for an enforcement policy. The same argument holds for the Medical School, even though it coordinates the research funds and administers the salaries of the hospital medical staff.

Within the hospital, the pharmacy department and the P & T Committee were examined as possible candidates for enforcing the program; the pharmacy department because of its ability to locate problems through its decentralized staff; the P & T Committee because of its relationship to the medical staff. A combination of the two provides the P & T Committee with the fact finding capabilities of the pharmacy department and produces the type of physician based enforcement required by the program.

One essential aspect of any program in which pharmacists assume responsibilities previously held by other people is reimbursement for the services provided. Funding can be divided into two areas; seed money with which to implement the program and finances with which to support the program on a continuing basis. Third party reluctance to reimburse hospitals for research endeavors eliminates the possibility of requesting the hospital to support the program with patient care funds.[19] The IRC, maintained through voluntary membership, does not have funds available to support pharmacy activities. Since the Medical School faculty and students are major recipients of the benefits provided by a pharmacy based investigational drug center, the Medical

19. Medicare and Medicaid Guide,"Research Costs", Reg. Sec. 405.22, Principle 1-5, par 5400, May 1975.

School is a logical source form which to seek funds. Medical School support for research is a one time "get you going" type of support, and therefore can only be considered as a source of seed money.[20] Hospital medical departments (Surgery, Medicine, etc.) are another alternative from which to obtain initial support for the program. Donations from each department, based on the number and complexity of studies performed by physicians in the depatment, provide coverage for pharmacy costs associated with studies performed by department members.

Most medical departments are reluctant to provide continued support for the program in this manner.[21] Department heads favor a "fee per study" system. Pharmacy developes a budget for each study in which they are involved, reflecting the costs associated with coordinating that study. This budget becomes a part of the investigator's grant proposal to the sponsoring pharmaceutical company. An important concern with this type of reimbursement system is timing. Budget proposals must be submitted to investigators prior to the completion of grant proposals. Early involvement of pharmacy in the investigational drug process assures the feasibility of this type of compensation.

One source of support which proved less promising than it appeared initially, was the pharmaceutical manufacturers. In 1975, the Pharmaceutical Manufactures Association (PMA) distributed a statement which was presented as its policy on investigational drug studies.[22] It expressed many of the same ideas and concerns experienced with the traditional method of conducting

20. Vinti,R.A., op.cit.

21. ibid.

22. PMA, op.cit.

clinical drug research at UWH. Because of the potential benefits to pharmaceutical manufacturers from a centralized coordination program, letters requesting support for the development and implementation of the pharmacy based system were sent to the PMA and two drug companies involved extensively in drug research (Appendix B). The PMA is yet to respond, and the negative criticisms about the program received from the drug companies demonstrate their lack of knowledge about the current practice of hospital pharmacy and institutional problems associated with investigational drugs.

The manner by which pharmacy gets involved with the drug control aspects of an individual study is a delicate political issue. Physician-investigators may be reluctant to delegate the responsibility of investigational drugs used in research projects. Mandatory pharmacy involvement with every investigational drug study fosters unrest and disapproval among a proportion of physician-investigators because of the additional restriction imposed by the hospital on the physicians' right to practice. Voluntary use of the pharmacy department by investigators is an ineffective method. University Hospitals pharmacy department relied on this mechanism prior to the new investigational drug program, and was only involved with three of the forty-four investigational drug studies performed in the hospital at that time.[23]

Use of the pharmacy department as a resource, to assist investigators in satisfying the drug control requirements adopted by the hospital, is an effective means to obtain pharmacist involvement in clinical research. Investigators must contact the pharmacy if they require assistance in meeting these requirements. Since University Hospitals' investigational drug program became effective in November 1976, the pharmacy has taken an active

23. Vinti, R.A., op.cit.

role in seventeen drug studies, and in July 1977 will obtain twenty-seven additional studies from the Oncology Department.

Benefits of Pharmacy Involvement

The policy and procedure developed by the pharmacy department and P & T Committee, and eventually adopted by the hospital board and CPHS, is shown in Appendix C. The essential aspects of a pharmacy based investigational drug center; early involvement of pharmacy in the process, creation of a liaison between the P & T Committee and CPHS, establishment of minimum standards of practice, and incorporation of enforcement procedures have been included in the document. Anticipated outcomes of the investigational drug program will benefit all personnel involved with clinical drug research. Pharmaceutical manufacturers, sponsoring investigational drug studies, will have a centralized agent for:

1) obtaining information about physicians interested in doing investigational drug research,
2) coordinating drug study information storage and dissemination,
3) receiving investigational drugs and maintaining adequate inventories,
4) maintaining records,
5) controlling investigational drug distribution,
6) providing additional monitoring capabilities for compliance to company study protocol,
7) providing clinical pharmacist monitoring of related therapy and adverse reactions in study subjects, and
8) coordinating the transfer of study drugs to other institutions for use by co-investigators.

With physicians spending less time on the tedious drug control aspects of clinical research, there is a potential to attract more investigational drug studies into the hospital. Central coordination also developes a pool of research expertise within the hospital, which provides prospective medical-legal protection to the institution, and can be utilized by the IRC in its evaluative and monitoring procedures. Central coordination creates one area within the hospital which may be contacted by personnel should drug study questions or problems arise. The organization provided by such a system produces a relaxed but guarded atmosphere within the hospital toward investigational drug use.

Investigators will be recipients of the benefits produced by the system. The availability of one center within the hospital through which information about procedures and requirements of clinical research can be obtained, and administrative and clerical responsibilities of drug studies handled, increases the investigator's time available for additional research and clinical evaluation of study patients. Ultimately, the patient benefits from the regulations, safeguards and shifts in responsibilities created by such a hospital system.

Description of Program

Development of a pharmacy based investigational drug center requires revamping many of the traditional procedures and relationships in order to accomodate pharmacy services designed to alleviate the problems associated with the conventional system. Besides the change in membership of the CPHS and its relationship to the hospital P & T Committee, alterations in forms and procedures used in the study approval process were necessary. The

pharmacy department was instrumental in modifying the information required by the CPHS for drug entities administered during studies. This resulted in a revised format for reporting information about proposed studies to the CPHS (compare Appendices D and E). The flow of the approval and monitoring process was altered somewhat, as evidenced by Appendices F and G, with hospital pharmacists potentially assuming a significant role.

Modification of internal pharmacy organization and procedures also was necessary to enable the department to provide the services offered to investigators. Personnel would have to be dedicated solely to the investigational drug program. To determine the staffing requirements of such a program, four institutions providing pharmacy services to investigators were contacted.[24] The number of studies and the extent of pharmacy involvement with the studies at these institutions was compared to the anticipated number of studies requiring pharmacy involvement and the pharmacy services offered at University Hospitals. Based on this information, the pharmacy department will require one full time equivalent (FTE) pharmacist and a 0.5 FTE typist to supply successfully the services offered in section A2 of the Policy and Procedure for Investigational Drug Control. Currently, one FTE pharmacist is working forty percent of the time with the investigational drug program. With the number of studies coordinated by the department increasing, the need for additional personnel time is becoming evident.

The pharmacy personnel involved with the investigational drug procedures are responsible for coordinating all pharmacy activities associated with the program. The development of procurement, packaging, labeling and dosage formulation procedures for individual drugs and coordinating these procedures

24. The institutions contacted were: M.D. Anderson Hospital and Tumor Institute, University of Kansas Medical Center, Clinical Center-NIH, and V.A. Hospital -Madison, Wi.

with the pharmacy department is a challenging and rewarding aspect of this position. It requires a review of the literature and the information supplied by pharmaceutical manufacturers to determine individual drug requirements.

The most time consuming aspect of the position is maintaining inventory control and patient records. Although systems have been developed to facilitate this activity (see Appendix H), the controls and records required by governmental and hospital regulations and individual study protocols demand close monitoring of the disposition of the drug to individual patients. Periodic audits on the perpetual inventory system and computer generated treatment lists, daily listings of patients receiving investigational drugs (Appendix I), provide necessary checks on the established systems to help assure the required accuracy of these records.

Probably the most satisfying component of the investigational drug pharmacist position is the provision of investigational drug information. The unique information base required by the position provides it with an expertise not found in any other area of the hospital. Requests from physicians, hospital personnel, the CPHS and the P & T Committee for information about investigational drugs and procedures can be channeled through this person. In this area the most important aspect of information coordination is disseminating appropriate information to authorized personnel involved in the ordering, transcription, and administration of investigational drugs. The pharmacy dedicated computer system assists the investigational drug pharmacist in this area. By abstracting information from articles and study protocols and entering it into the files of the computer system, the decentralized terminal screens can be utilized to disseminate study information.

Storage of this information in the computer files creates an easy and efficient mechanism for modifying and updating data. The computer also can generate hard copies of the information for posting on nursing units where an investigational drug may be utilized repeatedly (Appendix J). Another aspect of information coordination is the generation of drug disposition reports for investigators or drug companies as required by study protocol. Development of procedures for this activity is based on individual study needs.

Other responsibilities of investigational drug pharmacy personnel include the storage and distribution of forms necessary for initiating clinical drug research, maintenance of a current list of investigators and co-investigators authorized to prescribe an investigational drug and coordinating the other services offered to investigators by the pharmacy department in the hospital - Investigational Drug Control Policy and Procedure.

When developing a procedure, less confusion is generated when the new procedure is compatible with current procedures of the department. The pharmacy procedure for ordering an investigational drug for floor use was developed with the idea that the decentralized staff pharmacist's routine should be disrupted as little as possible. Therefore, dosage preparation and record keeping were centralized and the ordering process patterned after the current method of ordering FDA approved drugs.

Three additional activities are required of the pharmacist when an order is written for an investigational drug. Before the order can enter the pharmacy system, the pharmacist must check for a signed consent form in the patients chart. Informed consent is a federal requirement.[25] It was

25. 21 CFR 310.102.

established to enable patients to make educated decisions about becoming study subjects.[26] The check provided by the pharmacists helps protect the physician, pharmacy department and hospital from problems that may develop from lack of consent.

The decentralized staff pharmacist is responsible for calling the investigational drug pharmacist before obtaining the initial dose for a patient being started on an investigational drug, or when a patient is taken off a study drug. This provides an efficient mechanism for updating patient and drug disposition records and allows the investigational drug pharmacist to provide any randomization required by study protocol before a drug is started.

If a dose of an investigational drug is not administered for some reason, the investigational drug pharmacist must be informed so that appropriate records can be adjusted. This is accomplished by returning unused doses to the investigational drug pharmacist with an explanation of why the dose was not given.

When a prescription order for an investigational drug is received in the outpatient pharmacy, the drug is dispensed like an FDA approved drug. The only additional activities associated with the dispensing are checking for prescriber authorization and recording patient data on the perpetual inventory sheet, activities which are already performed for controlled substances. Delegation of minimal responsibility for the regulatory aspects of investigational drug studies to the staff pharmacist not only maintains the integrity of their daily routine, but also reduces the need for continued inservice on changes in governmental and hospital policies and

26. "Guidelines for the Preparation of Protocols for Review",CPHS-UW-Madison, unpublished, Jan. 1977.

procedures affecting these drugs. This also produces a small core of people to whom hospital personnel, physicians and committee members can relate.

The most appropriate method of reimbursement for pharmacy activities associated with an investigational drug study is a fee per study. Support for pharmacy is obtained directly from study grants benefiting through pharmacist involvement. The requirements of an individual study are discussed with the primary investigator for the study, and the extent of pharmacy involvement is determined. Using a predetermined pricing policy for services offered by the pharmacy department (based on the amount of pharmacist and typist time involved with each), a pharmacy budget is prepared for inclusion in the investigator's grant proposal to the study sponsor. A pharmacy based investigational drug center should become a self-supporting program utilizing this type of reimbursement plan, if enough studies are coordinated by the pharmacy department. Therefore, the pharmacy department must provide a high level of service that will appeal to investigators.

Evaluation

Acceptance

When evaluating the program, two areas must be reviewed - acceptance and performance. Physicians have accepted the program suprisingly well. There are, as with any control program, a few physicians who consider it an encroachment upon their prescribing rights, but physicians' rights are not restricted by regulations established by the program. The P&T Committee enforcement procedures protect the hospital by helping to assure that all clinical drug research is conducted in compliance with existing governmental and hospital regulations. The pharmacy based investigational

drug center serves only as a resource for physicians requiring assistance in meeting these requirements. Most physician - investigators can recognize the benefit of pharmacy coordinated drug control activities for investigational drug studies. Since the policy and procedure became effective in November 1976, the pharmacy has expanded its involvement in clinical research from a dispensing function to include providing most of the services offered in section A2 of the policy and procedure. The number of studies coordinated by the department also has increased from three to seventeen. Another indication of the positive attitude of the medical staff toward the program is the enthusiasm for the program shown by members of the Oncology Department. They are probably the only medical department within the hospital with adequate staff and funds to enable them to conform to all the drug control requirements of the program. Yet, they have requested the pharmacy department coordinate drug activities for all of the Clinical Oncology Group protocols. This would provide an additional twenty-seven studies to the pharmacy for coordination.

The CPHS provided the initial impetus for the development of a hospital system coordinating investigational drug activities. Now the pharmacy department works closely with the committee on monitoring compliance with governmental and hospital requirements and established study protocols. The CPHS has demonstrated its willingness to support the program by adopting the hospital policy into the committee's bylaws and delegating the responsibility of forms distribution to the pharmacy department.

Hospital personnel realize the advantage of a hospital center with investigational drug expertise. There is someone they can contact should questions arise about investigational drugs or study procedures. The centralized control mechanisms established for the program have provided more information to personnel involved with study drugs on the floor without disrupting the routines of nursing or pharmacy personnel.

With established drug control requirements and procedures for transferring investigational drugs to other institutions, hospital administration believed the institution was in a better position should FDA or Joint Commission for the Accreditation of Hospitals inspections of hospital research procedures occur.

Pharmaceutical manufacturers were the only group not receptive to pharmacy involvement with investigational drug studies. Comments received from to companies to which the program was presented, reflected apprehension with the ability of hospital pharmacy to provide the types of service required by clinical research. They feared the creation of a new administrative layer, which would only be after "a piece of the action"[27] between the company and the investigator. Drug companies seem unaware of the benefits derived from a close-working involvement with the institution in which the study is being performed. Hospital pharmacists must educate pharmaceutical companies about the current practice of pharmacy and the benefits

27. Personal communication with a pharmaceutical manufacturer, unpublished, Jan. 1977.

of pharmacy involvement with clinical drug studies if they expect future acceptance of a hospital-wide coordinated investigational drug system.

Performance

The pharmacy department has been able to respond to the needs of physician-investigators requesting assistance. Two investigators, sponsoring their own studies, were unable to obtain the drugs required in the study protocols until pharmacy department personnel contacted the companies producing the drugs and explained the situation. Two other physicians were refused hospital approval for their studies because of inadequate randomization for these studies. Another physician requested preparation of a protocol for a study he wished to conduct at the hospital. This protocol has been approved by the CPHS and the study will be initiated in January of 1978. The information sheets, developed to assist the dissemination of information to hospital personnel, have been widely accepted by the medical and nursing staff of the hospital. Pharmacists perform the literature search and abstracting and provide hospital personnel with an efficient means of obtaining essential information about an investigational drug study.

Conclusion

The confusion that exists by using various systems, developed by individual investigators, for controlling and distributing study drugs is eliminated by a pharmacy based investigational drug center responsible for coordinating a hospital-wide investigational drug program. Development of a system that meets the needs of a hospital is a long process, but once implemented it

is rewarding to see how extensive the demand for the program really was. Once physicians are aware of the benefits of pharmacy involvement in clinical drug research, the department should expect continued support from them.

Centralization of investigational drug activities within the pharmacy department is an inexpensive method of obtaining better drug control. Pharmacy budgets for individual studies approximate grant allocations for clerical personnel currently providing only drug control activities. Improved distribution and information systems can be maintained with the greater knowledge, experience and expertise in drug control possessed by hospital pharmacists.

The program is new enough that all potential areas of involvement have not been explored. Investigational drugs are used extensively, in house, for patients visiting the outpatient clinics, especially the Oncology and Hematology Clinics. Clerical staff are currently responsible for dosage preparation, record keeping and inventory control for all drugs, noninvestigational and investigational, used in these two clinics. The pharmacy department has not made an effort to become involved because of the volume of investigational drug use in these clinics and the department's inexperience with the new program. Pharmacy coordination of investigational drug activities in the clinics will require a pharmacist dedicated to the coordination of all drug activities therin. Clerical staff responsibilities for drug related activities then can be shifted to the pharmacist, and funding for the position obtained by eliminating clerical personnel from clinic staff.

Another problem incompletely addressed by the current investigational drug program is the investigational use of FDA approved drugs for non-approved

uses. The coordination of this class of clinical research requires mechanisms for drug control and record keeping differing from those used for studies of nonapproved drugs. Being informed about studies of approved drugs that do not conform to federal and hospital regulations is complicated by the physician's right to prescribe a drug product as professional judgement dictates. Unusual doses, uncommon regimens, and questionable uses may not indicate an investigational use of a drug product, but a physician's solution to a patient problem.

Clinical monitoring of patients receiving investigational drugs is the responsibility of the hospital's clinical pharmacists. Currently, information reported to the investigational drug pharmacist on side effects and problems encountered with research drugs has been minimal. With sufficient information now available through the computerized abstracts and files located in the hospital Drug Information Center, reports of clinical information about investigational drugs should increase.

Hopefully, a pharmacy based investigational drug center would stimulate an interest in research within the pharmacy department staff. This has not been evident to date. If hospital pharmacy is to be successful, it must be able to adapt to change. Research can develop the type of scientific thinking required to comprehend and originate innovative pharmacy services.

A pharmacy based investigational drug center operating within a hospital-wide investigational drug coordination program will improve the quality of research performed at the institution. Research quality directly affects the number of studies required by the FDA for proof of safety and efficacy. It also can affect the amount of risk to which subjects are exposed and, indirectly, the cost of clinical research to study sponsors. The effectiveness

of the pharmacy department in providing the services required by such a program will determine its success. Pharmacists have greater expertise in the area of drug control than any other personnel in the hospital. This provides sound rationale for coordinating investigational drug activities, like all other drug activities, through the pharmacy department. Then progressive pharmacy services can be applied to investigational drugs providing the necessary controls on these entities.

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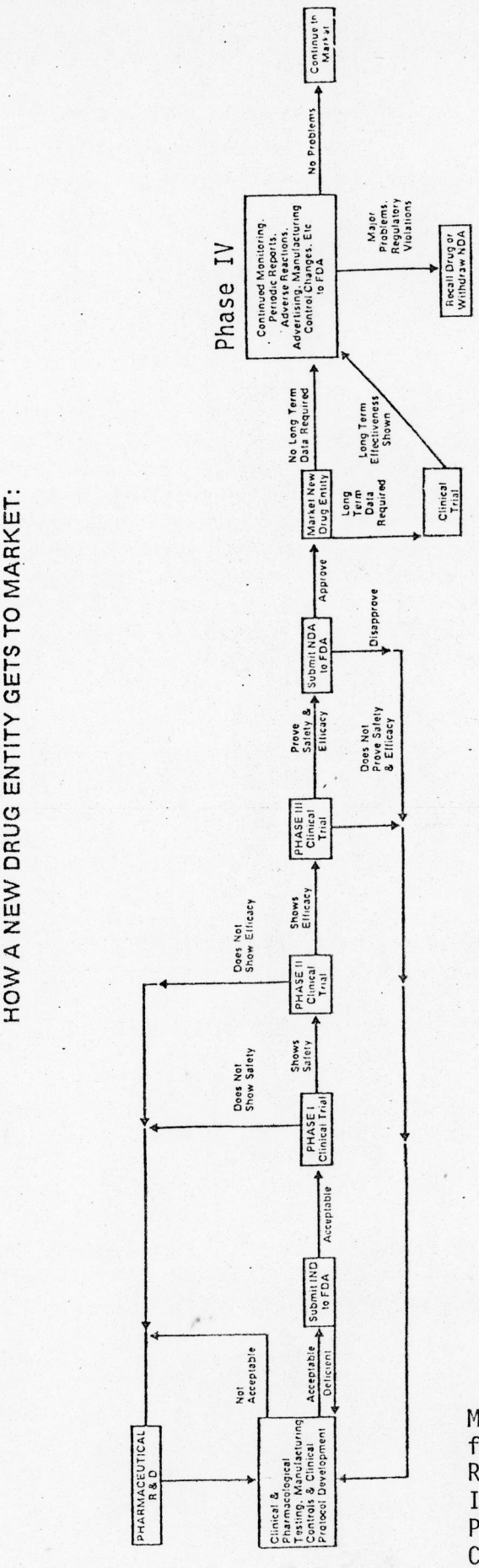


Modification of Diagram from Arbit, H.M.: Regulatory Aspects of Investigational New Drugs Presented at ASHP Midyear Clinical Meeting Anaheim, CA Dec. 1976.

Letter to P.M.A. and Drug Companies

University of Wisconsin Hospitals

CENTER FOR HEALTH SCIENCES
University of Wisconsin-Madison
1300 University Avenue • Madison, Wisconsin 53706

Dear Sirs:

The procedures and requirements necessary to perform an investigational drug study have become increasingly complex. The relationship of the investigator to the drug company, which has been direct and often independent in the past, has expanded to include close-working involvement with the institution in which the study is being performed. Professional organizations and federal agencies as well as local groups are requiring or recommending increased institutional responsibility which necessitates the development of a system integrating the clinical monitoring, distributive and organizational aspects of investigational drug studies. Unfortunately, standard policies and procedures have not been developed and tested to support a coordinated, flexible investigational drug control system.

University of Wisconsin Hospitals' Pharmacy Department is requesting support from the PMA for the development and implementation of a system that integrates these three aspects of drug studies. Since many PMA members are actively sponsoring investigational drug studies, we believe that PMA assistance in soliciting financial support from its members for implementing such a program is appropriate. The pharmacy based system for coordinating investigational drug studies in institutions would benefit pharmaceutical manufacturers from the availableility of methodologies and procedures which meet professional and federal standards. Also, because a pharmacy-based investigational drug coordination system can eventually be self-supporting by the prospective inclusion of its costs in all investigational drug study grants, both financial and control benefits will be provided PMA members in the future.

Administration of investigational drug studies has long posed a problem for the pharmaceutical manufacturer, investigators and institutions.

Pharmaceutical Manufacturers:

1. Companies spend vast amounts of time, effort, and money recruiting investigators to conduct drug studies in individual institutions.
2. Non-conformity to company study protocol produces questionable study results.
3. Adequate records are often not maintained.
4. Investigational drugs are often not stored or dispensed in a manner conforming to federal and state laws or institutional regulations.
5. Monitoring of study patients' related therapy and adverse reactions is often limited to the investigator.

Investigators:

1. Often have minimal knowledge of investigational drug study requirements.
2. Lack resources necessary to insure proper drug control and adverse to study protocols.

3. Have difficulty in finding study sponsors

Institutions:

1. Are leagally responsible for patients receiving investigational drugs.
2. Institutional Review Committees (IRC's), responsible for the initial approval and continuous monitoring of research studies must judge the acceptability of drug studies in terms of institutional regulations, relevant laws and standards of professional practice. Often the IRC's are not afforded the necessary expertise to evaluate drug related information and have no available resource to turn to for guidance.
3. Personnel involved with investigational drug order transcription and drug administration often lack essential information about the drug.

To some extent, these problems are common to all manufacturers, investigators and institutions. To alleviate some of the above problems, our proposed system employs procedures which promote efficient drug study initiation and complete and accurate study monitoring. We believe this approach is professionally desirable and cost effective.

This investigational drug coordination system, which may be appropriate to many institutions, is outlined on attached sheet.

Anticipated outcomes of the centralized investigational drug coordination system are:

1. Pharmaceutical companies, sponsoring investigational drug studies, have a centralized agent for:

   a. Obtaining information regarding physicians interested in doing investigational drug studies.
   b. Coordinating drug study information storage and dissemination.
   c. Receiving investigational drugs and maintaining adequate inventories.
   d. Maintain records.
   e. Controlling investigational drug distribution.
   f. Providing additional monitoring of compliance to study protocol.
   g. Providing clinical pharmacist monitoring of study patients' related therapy and adverse reactions.
   h. Coordinating the transfer of study drugs to other institutions for use by co-investigators.

2. Investigators benefit from the system:

   a. They are provided with a center from which to obtain research information and resources.
   b. Most of the administrative and clerical responsibilities of the investigator are handled more efficientyly by experienced personnel.
   c. The amount of time available to investigators for addtional drug studies and clinical evaluation of study patients increases.

3. The institution benefits from:

   a. The potential to attract more investigational drug studies into the institution.
   b. The development of a centralized pool of research expertise within the institution which provides prospective legal-medical protection to the institution.
   c. Hospital personnel involved in study drug order transcription and drug administration are provided with necessary information regarding administration, therapeutic and adverse effects associated with investigational drugs.
   d. IRC's are provided with assistance in the evaluation and continuous monitoring of investigational drug studies.

The patient ultimately benefits from the safeguards created by such a system.

The product of this program will be the development of a manual which outlines methods and procedures for instituting pharmacy-based investigational drug coordination. The PMA could share the manual with its members and participating institutions who are interested in having pharmacy departments involved in coordination of investigational drug studies. This should aid PMA members, investigators and institutions by reducing the developmental delays related to start-up by providing an efficient administrative and clinical control system, and by assuring the development of policies and procedures which comply with current FDA and individual institutional requirements. Policy and procedure updates, necessitated by the development of new federal regulations, can be made and routinely mailed through the PMA, so a continuing, reliable service is maintained.

An identical system to the one presented above has been adopted by the University of Wisconsin Hospitals medical board. To date, the pharmacy department has received requests from six investigators and one pharmaceutical manufacturer for assistance in study drug coordination. These requests support our feelings that the service offered in this system is necessary and in demand. We desire the resources necessary to adequately provide these services. Funding for a one year period of one full time equivalent pharmacist and one half time equivalent secretary (approximately $24,000) would allow the department to initiate the system and develop the manual. In the future, reimbursement for the support of pharmacy involvement in study coordination, can be be appropriated from individual study grants .

Implementation of the complete system is necessary to fulfill the department's responsibilities to the pharmaceutical manufacturers, investigators and institution. We earnestly ask that the PMA seriously consider organizing this funding endeavor.

Your interest and consideration in funding this project are most appreciated.

Sincerely,

David Zilz, Director
Pharmacy and Central Services

DZ:jp

	POLICY AND PROCEDURE	DATE EFFECTIVE: November 1, 1976	
UWH	UNIVERSITY OF WISCONSIN HOSPITALS	SUBJECT: INVESTIGATIONAL DRUG CONTROL	

I. PURPOSE: To assure a minimum level of practice that conforms to governmental and hospital regulations concerning investigational drug research performed at University Hospitals. (UWH)

II. POLICY: The Committee for the Protection of Human Subjects (CPHS), a Center for Health Sciences agency, must have two members from the hospital Pharmacy and Therapeutics Committee (P & T); one physician and one pharmacist, to provide hospital involvement in the approval process for investigational drug studies.

A. Mechanism for obtaining Investigational Drug Study approval:

1. Investigators must submit completed application forms (available from the hospital pharmacy department) and a protocol synopsis to the CPHS. Upon submission of an Investigational Protocol, the investigators must demonstrate, among other things, that they can comply with the requirements essential for drug control. The investigator must demonstrate the ability to:

a. Provide proper labeling for inpatient and outpatient use.

b. Maintain adequate supplies of investigational drugs and provide information concerning the source of the drugs in the hospital.

c. Provide for the accessability of investigational drugs when investigators are not available.

d. File drug information regarding pharmacology, side effects, dosage form, dilution requirements, packaging, rate of administration and other pertienent data in the hospital Drug Information Center.

e. Disseminate pertinent drug information to all personnel involved with the administration of an investigation drug.

f. Update the list of investigators and co-investigators continually and make the list available to personnel involved in the transcription of orders, distribution of the drug or administration of the drug. A copy of this list will be filed in the hospital Drug Information Center.

g. Keep adequate records to comply with all hospital and Food and Drug Administration (FDA) requirements.

h. Provide an inpatient distribution system compatible with the hospital's drug distribution system used for all FDA approved drugs.

i. Provide for the coordinated distribution of investigational drugs and information to other hospitals if the drug is to be used outside University Hospitals. The transfer of drug must be accomplished using mechanisms compatible with the other hospital's control, distribution, and approval systems.

2. If the investigators feel compliance with the above requirements would be difficult, they are encouraged to contact the hospital pharmacy department. This should be done prior to application for CPHS approval in order to determine which, of the services offered, will be needed to provide full compliance to all investigational drug regulations. The serivces offered by the pharmacy department are as follows:

a. Provide information and forms necessary for beginning an investigational drug study (FDA requirements, hospital requirements, etc.)

b. Consult with interested investigators on development of protocols.

c. Evaluate the literature and present expert opinion to the CPHS and the P & T Committee concerning investigational drug studies.

d. Obtain expert opinion from outside the CPHS or P & T Committee when necessary in deliberations.

e. Operate a center for investigational drug information which would disseminate appropriate information to all authorized personnel handling the individual drugs.

f. Aid the investigators in obtaining investigational drugs from the manufacturer.

g. Set up codes for blinded studies and make them available when the need arises 24 hour/day.

h. Determine packaging, stability and dosage form requirements for the durgs.

i. Maintain inventory, dispensing and other appropriate records.

j. Coordinate the transfer of investigational drugs to other hospitals through the appropriate channels, so they may be used by co-investigators in other hospitals.

k. Provide properly labeled, appropriately packaged investigational drugs for inpatients, outpatients and discharge use.

l. Obtain statistical reports on use of investigational drugs from the pharmacy computer system.

m. Provide additional monitoring capabilities to the CPHS and investigators.

3. The CPHS has three options:

a. Approve the investigational drug study as written, or with minor changes, for performance at UWH.

b. Refer the study to the P & T Committee if the hospital representatives feel there is a need for this action (eg. Questionable compliance to drug control requirements or existence of a special expertise on the P & T Committee pertinent to the study)

c. Deny approval of the study as written.

4. Investigators will be notified of the decision of the CPHS.

B. Non-compliance with Investigational Drug Control Requirements:

1. If physicians, pharmacists or nurses working at University Hospitals become aware of non-compliance by investigators regarding the internal control requirements in the use of investigational drugs, the specific cases should be communicated to the P & T Committee for appropriate action.

APPENDIX D

Traditional CPHS Application Form

UNIVERSITY OF WISCONSIN CENTER FOR HEALTH SCIENCES

Madison, Wisconsin 53706

CLINICAL RESEARCH PROPOSAL No. _____

To be supplied to the Committee for the Protection of Human Subjects prior to the initiation of any investigations involving human subjects or human materials, including studies in the behavioral and social sciences, whether grant supported or not. The original plus 20 copies should be sent to Sharon Riley, Room 701 WARF Office Building.

(Please Type) Date _____

Project Title: _____

Support or Sponsorship by:

Federal Agency _____ Federal Grant # _____

Non-Federal Agency _____ Grant # _____

Other (Please Specify) _____

None _____

Is granting agency awaiting notice of approval by this committee? Yes ___ No ___

Principal Investigator _____

Department _____ Rank _____

Campus Mailing Address _____ Telephone _____

Faculty sponsor required if investigator is below rank of instructor:

Sponsor (if required) _____ Telephone _____

Physician responsible for procedures, if other than the principal investigator:

Name _____ Department _____ Telephone _____

1. Does your proposal involve the use of human subjects or human material? Yes ___ No ___

   If the answer is no, completion of form not necessary.
   If the answer is yes, please complete remainder of form.

2. Summarize the hypothesis and/or objectives of the research or demonstration project including a statement of the methodology to be used, statistical design where appropriate, and a summary of the relevant literature in the area of interest. Please be specific, e.g., administration of drugs, biopsies, frequency of blood samples and instrumentation.

3. If drugs are to be administered, complete the following:
   Does the drug you intend to use have F.D.A. approval? Yes ___ No ___
   a. Is the drug you intend to use commercially available? Yes ___ No ___
   b. If no, does the drug have IND approval? Yes ___ No ___
      If yes, the IND # is _____
   c. If not a. or b., are you planning to file for IND#? Yes ___ No ___
   d. If the drug is approved, is it approved
      i. at the dose level you plan? Yes ___ No ___
      ii. for this purpose? Yes ___ No ___
      iii. at this site or by this means of administration? Yes ___ No ___

4. Describe
   a. How and by whom subjects are selected?
      -- Are they patients? From what hospital and service? How have you provided for informing the attending physicians of the research project?
      -- Are the subjects "normals", volunteers, paid (how much)?
      -- Are they minors, students of the investigator, fetuses, abortuses, pregnant, prisoners, mentally infirm or mentally disabled?
      -- How many subjects will be recruited?
   b. What risks are involved for the subjects?
   c. Are the proposed procedures part of or coincident with diagnostic or therapeutic procedures?
   d. What measures will be used to protect the rights and welfare of the subjects?

5. Provide a sample of your proposed form for obtaining informed consent. Please take care that all elements of informed consent as described in the attached guidelines are adequately dealt with. In addition, please consider the following:
   a. The consent form itself must be explicit about procedures, risks, benefits and possible discomforts. It is not sufficient for the written format to merely allude to a verbal explanation of these by the investigator.
   b. The consent form can not contain any language that could be viewed as persuasive or coercive, e.g., "These procedures have the approval of the Health Sciences Center Human Subjects Research Review Committee."
   c. The consent form should not include an "anti-waiver" statement such as "I do not waive any of my legal rights or release the University of Wisconsin or its agents from any liability for negligence."

Date _____ Signed _____
Principal Investigator

Date _____ Signed _____
Sponsor, if required

Date _____ Signed _____
Physician, if required

Date _____ Signed _____
Department Chairman

Note: It is understood that any changes in the protocol as described herein must be reported to and approved by the Committee prior to inception of the change. Use the form "Notice of Change of Protocol".

COMMITTEE DETERMINATION: SUBJECTS..... AT RISK _____ NOT AT RISK _____

Committee Action: Approved _____ Deferred/Not Approved _____

Approved with the modifications as specified: _____

_____

Date _____ Signed _____
For the Committee

ne - rev. 12/75

GUIDELINES FOR INFORMED CONSENT

The basic elements of informed consent are:

1. A fair explanation of the procedures to be followed, including an identification of those which are experimental.
2. A description of the attendant discomforts and risks.
3. A description of the benefits to be expected.
4. A disclosure of appropriate alternative procedures that would be advantageous for the subject.
5. An offer to answer any inquiries concerning the procedures.
6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.

In addition, the agreement should contain no exculpatory language through which the subject is made to waive, or appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.

INFORMED CONSENT FOR RESEARCH USING QUESTIONNAIRES

1. As response to an anonymous questionnaire per se constitutes consent of the respondent, no written consent form is required.

2. If a questionnaire requires the respondent's name, the final page of the questionnaire should contain the brief statement, "I have voluntarily provided information on this questionnaire with the understanding that my answers will become part of an anonymous data file and that questionnaires will be destroyed." This would be followed by a space for the respondent's signature.

3. The respondent should be informed in the cover letter for both anonymous and nonanonymous questionnaires about:

   a. Who is conducting the research
   b. To whom the research will be reported
   c. Who will be answering the questionnaire
   d. The general purpose of the study

A COPY OF THE CONSENT FORM SHOULD BE PROVIDED FOR RETENTION BY THE SUBJECT

APPENDIX E

Revised CPHS Application Form

UNIVERSITY OF WISCONSIN-MADISON, CENTER FOR HEALTH SCIENCES

COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

PROTOCOL FOR RESEARCH INVOLVING HUMAN SUBJECTS

CPHS # _____

To be submitted to the Committee for the Protection of Human Subjects prior to the initiation of any investigation involving human subjects or human material. The original plus 24 copies should be sent to Sharon Riley, CPHS Executive Secretary, 1007 WARF Office Building.

I. FACE SHEET

(please type)

Date _____

Project Title: _____

_____

Supporting Agency (if applicable) _____

(Name) (Grant number)

Principal Investigator: _____

(Name) (Rank)

_____

(Campus mailing address) (Department) (Telephone)

Faculty sponsor if below rank of Instructor: _____

(Name) (Telephone)

SIGNATURES: Principal Investigator _____

Department Chairman _____

Faculty Sponsor (if required) _____

CPHS USE ONLY

COMMITTEE DETERMINATION: Human Subjects: AT RISK _____ NOT AT RISK _____

APPROVAL DATE: _____

SIGNED: _____

(FOR THE COMMITTEE)

REAPPROVAL DATE: _____

REAPPROVAL DATE: _____

II. DESCRIPTION

A. Purpose: (refer to guidelines page 5)

B. Duration of project: (guidelines page 6) From _____ to _____

C. Subject selection: (guidelines page 6)

numbers of subjects _____ numbers of control subjects _____

how subjects are to be selected _____

_____

_____

material inducements _____

The protocol proposes to include as subjects:

	Yes	No		Yes	No
pregnant women	_____	_____	fetuses	_____	_____
mentally infirm	_____	_____	abortuses	_____	_____
mentally retarded	_____	_____	minors	_____	_____
hospitalized patients	_____	_____	prisoners	_____	_____

D. Specific location of study: (guidelines page 6)

_____

E. Background: (guidelines page 6)

F. Research design (guidelines pages 6 and 7)

PREPARE ON SEPARATE SHEETS

III. HUMAN SUBJECTS

Please refer to guidelines page 7. The general headings must be followed.

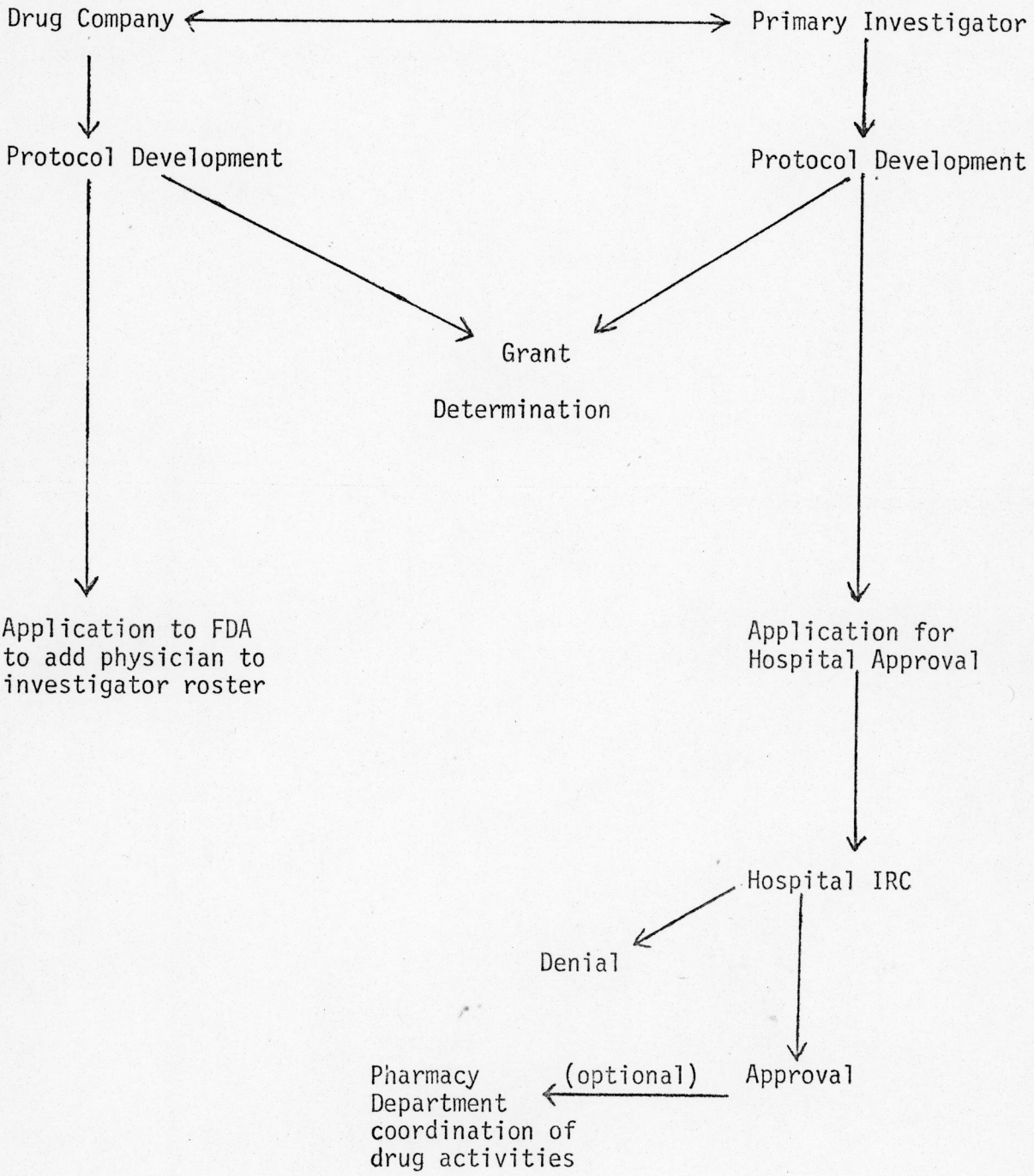
A. Subject population
B. Potential risks
C. Consent procedures
D. Protection of subjects
E. Potential benefits
F. Risk-benefit ratio

IV. INFORMED CONSENT

Please refer to guidelines pages 7-12. Submit a copy of the consent form and all materials used in the recruitment and selection of subjects.

APPENDIX F

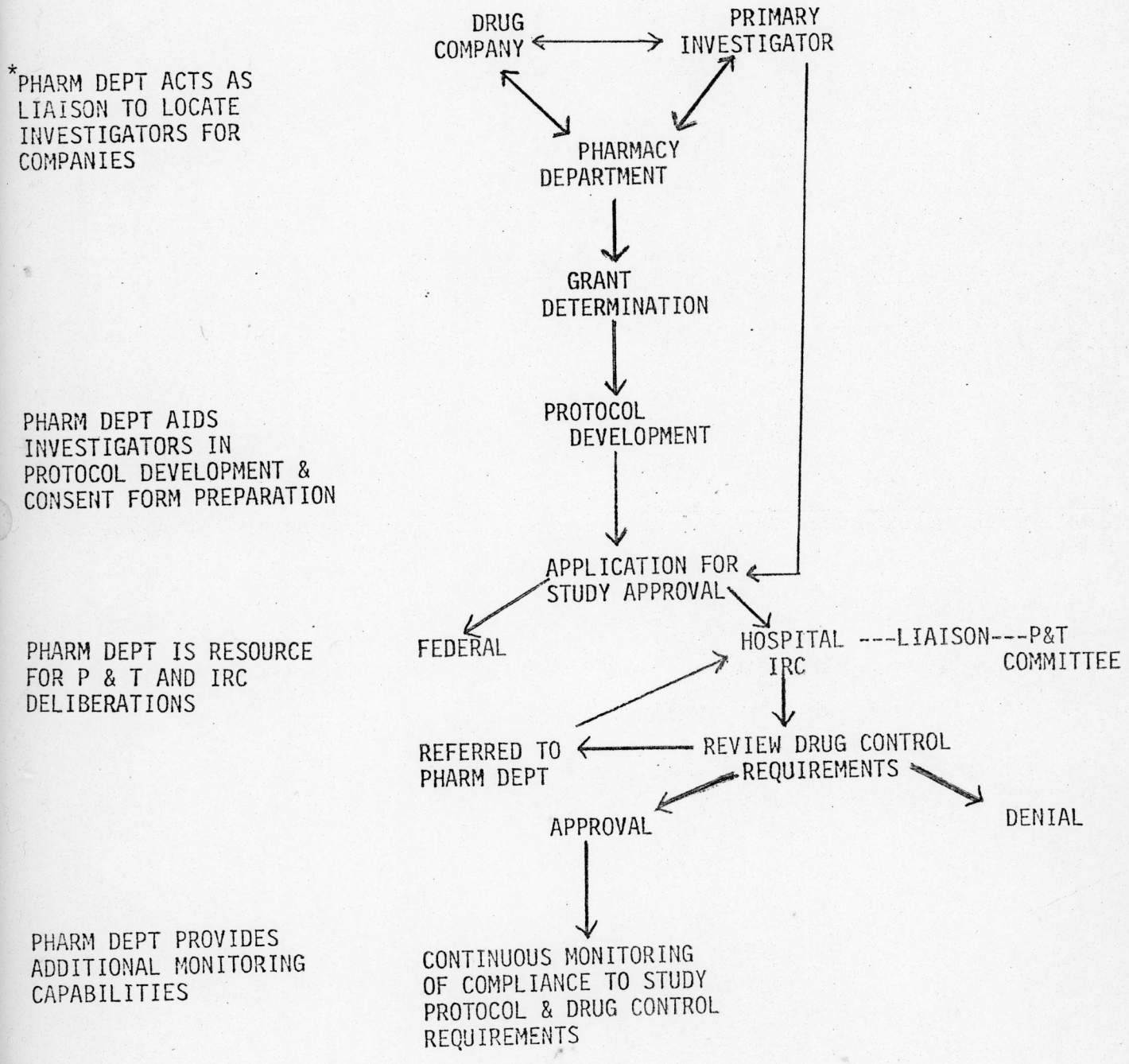
TRADITIONAL FLOW DIAGRAM FOR INVESTIGATIONAL DRUG PROCEDURE AT U.W.H.



APPENDIX G

REVISED

FLOW DIAGRAM FOR INVESTIGATIONAL DRUG PROCEDURE AT U.W.H.



*Indicates pharmacy activites at appropriate levels in the process.

APPENDIX H

Current UWH Pharmacy Department Investigational Drug Use Sheet

Drug/Streng[th]/Dosage Form ____________ Protocol No. ____________ Princp. Inv. ____________

Inpt.	Outpt.	Protocol or Drug	Date Start Stop	Pt's Name and Unit	Rx No.	History #	MD Ordering	Dose Schedule	Quant.	Manuf. & Lot#	Omitted doses Reasons

CURRENT UWH PHARMACY DEPARTMENT

INVESTIGATIONAL DRUG INVENTORY SHEET

DRUG/Protocol _____

Lot # _____

Balance _____

TE	ISSUED TO	QUANTITY ISSUED	REMAINING

AREA _____

APPENDIX I PAGE 01

Sample UWH Pharmacy Department 2300 14MAY77

Treatment List

BECKER STANLEY 267384 2WST 229W02 DR. DAVIS
PROBLEMS: PROSTATE CA WITH METS ADMITTED: 05MAY77
ALLERGIES:N.K.D.A.

ORDER # 22 ORDERER: PHARMACIST:LST LAST MOD: TECH:
CODE:1856 ESTRAMUSTINE(PHOS)CAP 420MG PO START:1800 14MAY77
BID STOP:1200 17JUN77
DOSES GIVEN: 1 MULTI-DOSE COUNT: 0 COST: . 1
ATTRIBUTES: 8
SELH
HOURS: 8 18

ORDER # 23 ORDERER: PHARMACIST:LST LAST MOD: TECH:
CODE:1856 ESTRAMUSTINE(PHOS)CAP 280MG PO START:1200 15MAY77
QDAY STOP:1200 18JUN77
DOSES GIVEN: 0 MULTI-DOSE COUNT: 0 COST: . 1
ATTRIBUTES: 8
SELH
HOURS:12

MULCAHY DAVID 791246 6BRN 6BRN02 DR. DEMLING
PROBLEMS: 30% BURN (2 AND 3RD DEGREE) ADMITTED: 26APR77
ALLERGIES:NKD

ORDER # 3 ORDERER: PHARMACIST:BRC LAST MOD:RLD TECH:
CODE:1561 ANTIBIOTIC BWL PRP STDY B1 5ML PO START:2200 26APR77
TID STOP:1200 30MAY77
DOSES GIVEN: 3 MULTI-DOSE COUNT: 0 COST: .2000
ATTRIBUTES:
SELH
HOURS: 6 14 22

ORDER # 4 ORDERER: PHARMACIST:BRC LAST MOD: TECH:
CODE:1562 ANTIBIOTIC BWL PRP STDY B2 20ML PO START:1600 26APR77
QID STOP:1200 30MAY77
DOSES GIVEN: 4 MULTI-DOSE COUNT: 0 COST: .3200
ATTRIBUTES:
SELH
HOURS: 6 10 16 22

[1 INSL 2 UNC 3 INJ 4 UNST 5 ORAL 6 7 8 9 M-D]

MEDICATION ORDER RETRIEVAL CONTINUE ON PAGE 02

ORDER # 5 ORDERER: PHARMACIST:BRC LAST MOD:KDL TECH:
CODE:1563 ANTIBIOTIC BWL PRP STDY B3 12.5MLPO START:1600 26APR77
QID STOP:1200 30MAY77
DOSES GIVEN: 4 MULTI-DOSE COUNT: 0 COST: .3200
ATTRIBUTES: 5
SELH
HOURS: 6 10 16 22

APPENDIX J
Sample UWH Pharmacy Department Investigational Drug Monograph

5 - A Z A C Y T I D I N E

VESTIGATIONAL DRUG STUDY - PROTOCOL NO. 76-632-230

RPOSE
THERAPY OF PREVIOUSLY TREATED ADULTS WITH ACUTE NON-LYMPHOCYTIC LEUKEMIA (ANLL) WITH 5-AZACYTIDINE.

INVESTIGATORS
PRINCIPAL: DR. JAFFE, JEFFERY P. 2-3188
ASSOCIATES: DR. RAICH, PETER C. 2-3188
HEMATOLOGY STAFF
HEMATOLOGY FELLOWS

EMISTRY
A PYRIMIDINE NUCLEOSIDE ANALOGUE OF CYTIDINE.

ECHANISM OF ACTION
ANTIMETABOLITE THOUGHT TO EXERT ITS ANTINEOPLASTIC EFFECT THROUGH AN INTERFERENCE WITH NUCLEIC ACID METABOLISM. IT IS PHOSPHORYLATED AND INCORPORATED INTO BOTH DNA AND RNA POLYNUCLEOTIDES OF VARIOUS BACTERIAL AND ANIMAL TUMOR SYSTEMS.

SORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
PLASMA T 1/2 = 3.5HR. GREATER CONCENTRATION OF DRUG IN TUMOR TISSUE THEN NONMALIGNANT TISSUE. 90% OF DRUG EXCRETED IN THE URINE WITHIN 24 HOURS.

ES
A CHEMOTHERAPEUTIC AGENT USED IN ACUTE MYELOGENOUS LEUKEMIA, AND HAS DUCED REMISSIONS IN SOME REFRACTORY CASES. IT HAS BEEN USED IN ACUTE LYMPHOCYTIC LEUKEMIA, CHRONIC MYELOGENEOUS LEUKEMIA, AND MULTIPLE MYELOMA WITH MINIMAL RESPONSE.

AUTIONS
THE MAJOR TOXICITIES HAVE BEEN GASTROINTESTINAL, HEMATOLOGIC, AND HEPATIC. NAUSEA AND VOMITING HAS AN OVERALL INCIDENCE OF ABOUT 70% AND BEGINS 1 1/2 TO 3 HOURS AFTER INTRAVENOUS INJECTION, AND RECURS WITH EACH ADMINISTRATION. ANTIEMETICS HAVE HAD VARIABLE EFFECTS, BUT SHOULD BE USED. CONTINUOUS ADMININSTRATION OVER 5 DAYS MAY REDUCE THE INCIDENCE. THE AVERAGE REPORTED INCIDENCE OF DIARRHEA HAS BEEN 53%, BUT HASN'T BEEN A DOSE LIMITING TOXICITY.
LEUKOPENIA OF <1500/MM3 WAS SEEN IN 34% OF THE CASES AND WAS DOSE RELATED. THROMBOCYTOPENIA HAS BEEN REPORTED IN 17% OF THE CASES AND IS DOSE RELATED. ANEMIA HAS BEEN AN INFREQUENT PROBLEM.
ABNORMAL LIVER FUNCTION TESTS IN 7% OF CASES AND ISN'T DOSE RELATED. MAY LEAD TO HEPATIC COMA AND CONTRAINDICATED IN PATIENTS WITH LIVER METASTASES AND SERUM ALBUMIN < 3G/DL.
NEUROMUSCULAR SYNDROME, FEVER, AND RASH HAVE ALSO BEEN NOTED.

RUG INTERACTIONS
NONE NOTED.

OSAGE AND ADMINISTRATION
200MG/M2 BODY SURFACE ADMINISTERED INTRAVENOUSLY IN THREE DIVIDED AILY DOSES FOR FIVE DAYS.

ATIENT INFORMATION
EXPECT NAUSEA, VOMITING, AND DIARRHEA. MONITOR FOR GENERALIZED MUSCLE TENDERNESS, WEAKNESS, AND LETHARGY.

TION
CYTIDINE INJECTION, 100MG WITH MANNITOL 100MG. WHITE LYO-
ZED POWDER.
E FOR 2 YEARS WHEN REFRIGERATED (4-10C) IN INTACT VIALS.
RECONSTITUTED WITH 19.9ML OF STERILE WATER FOR INJECTION
UT PRESERVATIVE. MAY BE FURTHER DILUTED WITH LACTATED
R'S INJECTION FOR OPTIMUM PH.
STITUTED SOLUTIONS HYDROLYZE AT ROOM TEMPERATURE AND SHOULD BE
WITHIN 30MIN. FURTHER DILUTION IN LACTATED RINGER'S INJECTION
DES AN OPTIMUM PH (6.37) FOR SOLUTION STABILITY. THIS SHOULD
ED WITHIN 2 TO 3 HOURS.
EM: BEN VENUE LAB.

NAL INFORMATION
E AVAILABLE FROM UWH DRUG INFORMATION CENTER...2-1315

PH PREPARED BY: MICHAEL COLLINS, R.PH.
BY THE DEPARTMENT OF PHARMACY
F UWH. UNIVERSITY OF WISCONSIN HOSPITALS

CES
S OF INT MED, AUG76, PP237-45.