Nurse Practitioners as Principle Investigators in Pharmaceutical Clinical Studies

By

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A manuscript submitted in partial fulfillment of
The requirements for the degree of

MASTER OF NURSING

WASHINGTON STATE UNIVERSITY
College of Nursing

May 1999
To the Faculty of Washington State University:

The members of the committee appointed to examine the clinical project of Debbra Gale find it satisfactory and recommend that it be accepted.

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Chair
NURSE PRACTITIONERS AS PRINCIPLE INVESTIGATORS IN
PHARMACEUTICAL CLINICAL STUDIES

Abstract

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The pharmaceutical industry spends over $14 billion each year in research and development (R&D). A large portion of this R&D is spent in clinical trials testing the safety and efficacy of new drugs. These clinical trials are conducted at universities and private hospitals, clinics, and by specialized companies known as site management organizations (SMOs).

Nurse practitioners have the opportunity to take advantage of this huge industry in the role of primary investigator or sub investigator, conducting studies in their office or clinic. Being part of pharmaceutical research is looked upon as being beneficial and desirable, offering additional care, specialized testing and access to state-of-the-art medicine. The Nurse Practitioner as an investigator can also benefit from pharmaceutical studies by increasing professional networking and income potential.

Organization is the key to a successful clinical study. Getting ready and organizing a study takes intense planning. Studies need to be set up, space made available, supplies obtained, and coordinators hired. Budgeting is another important part of study planning. To continue to do studies in most settings, they
need to be profitable. Finally, subjects need to be recruited. Subjects can either
come from an investigator’s practice or advertising. Both groups have been
found to be equally valuable, but advertised subjects will add an extra cost to the
study budget.

Documentation is critical. Inaccurate or incomplete source documentation
can make monitoring visits by the sponsoring company difficult or even cause a
sponsor to not reimburse for a subject due to inability to show appropriate
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Pharmaceutical studies can be beneficial to both Nurse Practitioners as
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The pharmaceutical industry spends over $14 billion each year in research and development (R&D). A large portion of this R&D is spent in clinical trials testing the safety and efficacy of new drugs. These clinical trials are conducted at universities and private hospitals, clinics, and by specialized companies known as site management organizations (SMOs).

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INTRODUCTION

Pharmaceutical research has evolved over the last 150 years from the use of uninformed subjects where possible harm or lack of treatment for the subject was often the norm to today where study subjects are not only fully informed, they have the benefits of additional care, specialized testing and access to state-of-the-art medicine (McCarthy, 1994). Being a research subject is no longer looked at as necessarily high risk, but as being very beneficial and frequently desirable. Often once a person has been a subject in a research study, they will search out another study as soon as the first one is completed.

The number of pharmaceutical research studies conducted each year is increasing and consequently the number of subjects needed to complete these studies required to take a new drug to market is increasing. In 1995 the pharmaceutical industry increased their research and development budget from $13.8 billion to $14.9 billion, an eight percent increase over the previous year (Pharmaceutical Research and Manufacturers of America, 1995). More than 100 new prescription drugs will be released in the U.S. in 1998 (R &D Directions, 1998a). There are currently 124 new drugs being investigated for HIV and AIDS, 179 for bacterial and viral infections, 684 for cancer and cancer-related therapies, 91 for diabetes, 81 hormone replacements, and 11 for smoking cessation along with about 3200 new drugs for other diagnoses in some phase of development (R & D Directions, 1998b).
Nurse practitioners, with their expanding roles, are often in a perfect position to be investigators in these studies, increasing the amount of care they are able to provide their patients while expanding their own professional network and personal income potential.

There has been an increase within the past few years in the number of publications related to pharmaceutical research. Missing in the literature is the integration of nurse practitioners into this clinical research process. One possible reason for this lack of literature may be the limited number of nurse practitioners currently taking part in pharmaceutical studies. Therefore, the purpose of this paper is to discuss the advantages and disadvantages for nurse practitioners conducting pharmaceutical studies and to provide some helpful information on how to get started.

STUDY PHASES

All new drugs start preclinically in the lab and with animal studies where safety and efficacy are tested and established; then the pharmaceutical company applies to begin testing in humans. Phase I studies test the drug on healthy human volunteers, except in HIV and oncology studies where patients for whom no standard treatment is available (rather than healthy volunteers) are used (Kodish, 1992). These studies determine safety, side effects and half-lives in the human body and usually include 20 to 80 subjects (Code of Federal Regulations, 1993). Often drugs are tested in forms, such as intravenous or intramuscular, which the producer never intends to market. Phase II testing
begins testing in subjects who have the targeted condition and helps to
determine drug efficacy. These trials usually compare the drug under
investigation to a standard treatment or placebo. They include around 100 to
300 subjects and take about two years to complete (Wierenga, 1993). Phase II
volunteers tend to be healthier than their counterparts with the same condition.
Phase III trials are much like phase II, except they are intended to mimic real life
use and are looking for the more uncommon side effects, as well as long term
effects. Phase III trials can have several hundred to several thousand subjects
and last about three years although they often run longer. Phase IV trials are
post-marketing studies to explore long term safety questions, develop new
indications or determine safety for over-the-counter use. They can be as easy
as, survey studies for clarification of labeling or, as complex as true experimental
design, double-blind clinical studies.

FINDING STUDIES

Finding a study or studies that fit a type of practice or a provider’s patient
population is the first step in getting started. A nurse practitioner can contact a
pharmaceutical company and find out what they currently have under study. To
narrow the search, a company who currently has many products in an area of
interest is very likely continuing development in the same area. One example is
Wyeth-Ayerst, who already has many products for women’s health, opened a
research facility in 1993 devoted exclusively to the study and development of
products for women (Levy, 1997).
Contract research organizations (CROs) are becoming more popular with pharmaceutical companies. CROs are hired by the pharmaceutical companies to organize and run their studies. These groups often work with several different companies and may have more than one study available for a certain condition. These CROs are another good contact for a nurse practitioner looking for pharmaceutical studies.

A nurse practitioner can also contact a site management organization (SMO). A SMO coordinates studies and hires investigators in different specialties. This may be a way for a nurse practitioner to get started prior to investing large amounts of time and hiring extra staff. The SMO will usually do all of the regulatory documentation, transcribing and other paperwork related to a study. This frees up the investigator to just see subjects and review related testing.

**BUDGET**

Prior to accepting a study, the nurse practitioner that wishes to become an investigator should make sure that it is financially feasible. Most contracts are written on a per subject basis. Before signing and accepting a contract, an investigator needs to go through each visit and assign a price to every procedure. It is often helpful to develop a flow sheet, which can be used for every study with the cost already determined for each procedure. Costs should be determined for exams, electrocardiograms, phlebotomy, and advertising.
Most studies have a central lab for all laboratory testing, but occasionally a study requires a test to be done at a local lab, which should be included when determining the budget. If using other personnel, like a research coordinator or transcriptionist, that cost needs to be determined including paperwork after the subject is gone and time spent with pharmaceutical personnel. Investigator time should also include time with pharmaceutical personnel and time spent reviewing laboratory tests when required. When working with an SMO, the investigator will usually have a contract with the SMO rather than the pharmaceutical company directly and is paid per visit determined by the procedures required by the investigator at each visit. Reviewing the budget prior to accepting a study is very important, especially if the investigator is working with a group and must justify the project. Both direct and indirect costs such as labor and supplies and indirect costs such as space and extra calls to study subjects need to be addressed. A drug study should benefit the practice, as well as the subjects if the investigator hopes to continue doing pharmaceutical studies.

RECRUITING SUBJECTS

Finding appropriate research subjects who accurately represent the projected treatment population is critical to ensure good clinical data. Government regulations are being relaxed, making it easier to get products to market at a record pace and pharmaceutical companies are spending more than ever on research and development (Novarro, 1997). Regulations put into effect
in 1994, also require inclusion of women and minorities in all appropriate studies (US Department of Health, 1994). This new regulation withdrew a long-standing policy that barred women of childbearing potential from all phases of clinical trials. This was justified by claiming protection for potential unborn children and the possibility of intrasubject variability during menstrual cycles and when using oral contraceptives (Wright & Chew, 1996). Up until this time, almost all studies were done on young and middle aged white men and it was assumed that the findings could be generalized to all genders, ages and races.

Recruiting potential subjects may be the most difficult part of running a pharmaceutical study. The number of studies being done and the number of patients enrolled in studies has increased drastically in the last few years. The number of subjects necessary for any one study has increased steadily by 5-7% annually, since 1989 and now the number of subjects needed for each drug to go to market averages about 4000 (Boston Consulting Group, 1994). This makes competition for subjects intense. Also, the inclusion and exclusion criteria for each study such as minimum diastolic blood pressures or fasting blood sugar levels is becoming more and more specific (Westrick, 1997). The sponsor may ask prior to placing a study with an investigator how many subjects the investigator thinks can be enrolled in a limited amount of time. Enrolling subjects and doing so quickly ensures the chance of doing future funded studies with the sponsor.
There are many ways to recruit subjects, including the investigator's own practice, referrals, advertising in newspaper, radio, television, or even the Internet. This last advertising strategy is becoming more and more important, as more Americans are accessing the Internet and it is estimated that about 15% of all Internet searches are for healthcare related issues for the user or a family member (CommerceNet, 1994). One study (Bielski & Lydiard, 1997) found an average of 87.2% of subjects in randomized clinical studies came from advertising with newspaper ads being the most common. All advertising must obtain institutional review board (IRB) approval. If an investigator intends to advertise, or even thinks that they might need to advertise to reach enrollment goals, development of materials should be done early and sent to the IRB with the first packet of regulatory material. Once advertising is placed, the number of subjects that respond should be tracked and the cost per subject enrolled for each advertising source determined. This will help an investigator in determining where to place subsequent ads for the most subjects in the least amount of time at the lowest per subject cost. Previous studies have shown little or no clinical difference in advertised subjects compared to subjects obtained from the investigator's practice (Amort & Lenox, 1989; Breckenridge, 1985; Covi, 1979; Hersen, 1984; Rappaport, 1995; Thase, 1984).

Other forms of publicity such as local news interviews about the topic, for plugging the study with a phone number at the end of the interview can help speed the enrollment process. Another way to get information about current
studies is to have information booths at local events such as the local Diabetes Association walk. This is a great way to contact a large number of people with a targeted condition with a limited amount of cost.

Cost for advertising is usually the responsibility of the investigator. Looking at options and where the largest number of subjects can be obtained for the least amount of cost is crucial to the financial success of a study site. One way to control costs is to know what kind of advertising will be needed prior to contracting with the sponsor realizing that certain populations are harder to recruit for and advertising costs run higher in metropolitan areas. These costs can be added into the proposed budget.

When advertising for subjects, the most important thing is to have the ability to follow-up with potential subjects, as quickly as possible. Not returning calls in a timely manner, loosing messages, or not being able to schedule a potential subject quickly can lose that person’s confidence in the investigator before you even get a chance to meet. An investigator must also remember that not all subjects who contact a site will be eligible for screening and of those screened, not all will be randomized. But, for those who do qualify, Bielski & Lydiard (1995) have shown, on average, 18.4% of subjects volunteer for a second study and 9.5% participate in a third.

INFORMED CONSENT

After subjects have been contacted and before any study procedures are conducted, informed, written consent must be obtained. When subjects are
enrolled, they must be informed of all the risks, responsibilities and benefits involved in participating in a research study. Obtaining written informed consent is a part of this process. It is important that the informed consent form contain the reason for the trial, all the risks involved, drugs the subject might be given, number of visits involved and any laboratory tests required. This consent form must also be written at the appropriate level so that laymen, with limited reading skills can fully understand the study. The investigator is responsible for reviewing the consent form with the subject to be sure that the subject understands all the elements of the study. Often having another person, like the study coordinator, also go over the consent with the subject can help with comprehension. According to Prentice, professor of cell biology and anatomy at the University of Nebraska Medical Center, "Consent without comprehension is not consent" (R&D Directions Staff, 1997).

SUBJECT RETENTION

Once subjects are enrolled, retention is very important to maintain the integrity of the study. There should rarely be a reason why a subject should be withdrawn after randomization (Cook, 1997) and all attempts should be made to insure complete follow-up of all subjects enrolled. Every subject who is lost after enrollment, risks the loss of important data and takes the chance of biasing the study findings. Several studies have been done that discuss the importance of subject retention in various types of trials (Demi, 1995; Wineman, & Durand, 1992; Rudy, Estok, Derr, & Menzel, 1994; Robinson, & Marsland, 1994; Beck,
1994). It is important, however, to always keep the subjects' best interest in mind and not to coerce any subjects who have chosen for personal reasons to discontinue. At all times, the subject's health and well being should be the investigator's number one concern. If the therapy being tested is causing medical complications or interfering with needed treatments, the subject should be removed from the study per protocol and appropriate follow-up should be arranged. In such cases, the reasons for any early terminations should be fully documented and final outcomes tracked.

DOCUMENTATION

Source documentation is crucial to any pharmaceutical study. Source documents are any form in which information is first captured. This can be the medical chart, a phone message, a patient diary, a lab report, or a post-it note®. Everything that you do or tell a subject must be recorded somewhere other than the final sponsor forms (case report forms or CRFs). The rule is, if it isn't written down, it didn't happen. The source documentation should support the CRF, not the other way around. This information must also be in its original form, with no obliterating data, crossing out, white out or recopying. Any changes to the source documents must be initialed and dated to show when the change occurred. Study staff are usually not allowed to change certain documents such as subject diaries. Any changes or corrections in subject diaries need to be initialed and dated by the subject. When obtaining source
documentation it is also important to be sure that all the information required by
the CRF be original documents.

It may seem desirable to copy the CRFs and use these copies for source
documents but most sponsors do not allow this practice. Customized forms with
check boxes can be made to help the investigator and their staff remember to
complete all the procedures required for a study visit. These forms also become
source documentation and need to be retained with the subject's chart.
Thorough and accurate medical documentation is always an important part of
practice, but this will be painfully clear if histories are unclear, sketchy or
inconsistent when trying to determine if a subject is appropriate for a study or
when a sponsor is reviewing information.

STUDY COORDINATORS

Investigators often find that the amount of work involved in organizing and
conducting a pharmaceutical study can be overwhelming especially if conducting
more than one study at a time. What many investigators do is hire a clinical
research coordinator or CRC. The CRC can have any background; although
when hiring a CRC, choosing a registered nurse (RN) may make doing studies
easier since they have the basic background of the conditions being studied.
Some studies even require the coordinator to be an RN although this is often
study or sponsor specific. The CRC should be detail oriented, motivated to work
alone and if doing hospital studies, have the ability to work with and motivate
others. Here again, the use of an RN in in-hospital studies may help put the
staff nurses at ease. The CRC should take on all the extra responsibilities associated with the study such as scheduling, receiving supplies and recruiting. Isaacman and Reynolds (1996) documented a successful enrollment rate increase from 14% to 50% in one year with the addition of a research nurse. This study also showed an agreement between the nurse and investigator on eligible subjects of 97.5 percent. Although the ultimate responsibility of running a study belongs to the investigator, many of the duties can be given to someone who is hired full or part time or on contract to assist with the studies.

AUDITS

When doing a study, the sponsor, the FDA or both may audit an investigator. Sponsor audits determine if there are any problems within a study at any or all sites. Often sites chosen for sponsor audits are who enrolled larger numbers of subjects, sites who are new to the sponsor, those sites which a monitor has voiced concern with, or the selection can be purely random. The sponsor may also choose sites that may be most likely to be audited by the FDA. Sites that the FDA most often audit are high enrollers, sites new to research and sites in which the investigator is not a specialist in the area being studied. These audits may seem a nuisance at the time but, can often benefit the investigator. If an investigator does well at an audit, a pharmaceutical company may be more inclined to contact the investigator again for future studies.
DEVICE STUDIES

An option, if time and resources are limited at a possible investigator’s site is a device study. Device studies are often organized differently than drug studies and have limited regulations. The largest numbers of device studies in this country are considered by the FDA to be exempt or nonsignificant risk and require little or no regulatory documentation. IRB approval or informed consents are not required unless required by the investigator’s institution. Protocols are not always required but may be used as this is a good business practice. It also helps describe the experiment to be done and what is expected of the investigator. Investigator records may also not be required but, as mentioned earlier, it is always good clinical practice and records should be kept. Investigator agreements are also not required, although expectations are clearer when they are in place (Stark, 1997).

Another option to doing studies when time and resources are tight, is to work with a site management organization (SMO). A SMO is a coordinating group who can come into an investigator’s office and manage the study and provide the coordinator and regulatory documentation. Sometimes another option would be that the investigator could go to the SMO office to see subjects. Working with an SMO is a good way for investigators to do research, when they are new to research or if limited on time, staff or space.
CONCLUSION

Pharmaceutical research is a 14 billion dollar plus industry in which both nurse practitioners as investigators and their patients can benefit from the additional care and state-of-the-art medicine for subjects and increased income and networking for nurse practitioners. There are many ways to get started, contacting a drug company directly, a CRO, or an SMO. Organization at the beginning is key to a study's success. Hiring knowledgeable staff, efficient subject recruiting and good source documentation will also make a study run smoothly and benefit all involved.

Research in pharmaceutical studies is a growing market, which has been under represented by Nurse Practitioners. With the current opportunities and benefits available to Nurse Practitioners and their patients, this is a market that all Nurse Practitioners should at least consider and if given the option to do studies, take a serious look at the possibilities.
REFERENCES


Changing Environment for US Pharmaceuticals (Boston Consulting Group, Boston, 1994).


