

ACCP WHITE PAPER

Research in Women and Special Populations

American College of Clinical Pharmacy

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The American College of Clinical Pharmacy charged a Task Force on Research in Special Populations to review, update, and broaden its 1993 White Paper, *Women as Research Subjects*. Participants of the task force included pharmacy clinicians and investigators in the field. This resulting White Paper, *Research in Women and Special Populations*, discusses the current concepts regarding the conduct of research in women, as well as in special populations (children, the elderly, minorities, the cognitively impaired, and other vulnerable populations such as prisoners and refugees). For each specific population, the barriers to research participation, current guidelines and regulations, and available recommendations to address these barriers are discussed. The participation of research by these populations requires addressing special social and ethical challenges. Clinical pharmacy researchers should be cognizant of these guidelines and be an advocate for the inclusion and the rights of women and special populations in research participation.

(*Pharmacotherapy* 2008;28(9):93e–113e)

In 1993, ACCP published the White Paper, *Women as Research Subjects*.¹ Since that time, significant changes, including new regulations regarding the conduct of research in women and other special populations, have occurred. In 2004, the ACCP Publications Committee conducted a review of the 1993 White Paper and recommended that it be revised and updated.

This document was written by the Task Force on Research in Special Populations, commissioned by ACCP: Kai I. Cheang, Pharm.D., BCPS, Chair; Carol Ott, Pharm.D., BCPP; Sandra Garner, Pharm.D., BCPS; Hope Campbell, Pharm.D., BCPS; Laura Hansen, Pharm.D., BCPS, FCCP; Qing Ma, Ph.D.; Elaheh Nazeri, Pharm.D.; Karen Gunning, Pharm.D., BCPS; Daniel Wermeling, Pharm.D. Approved by the American College of Clinical Pharmacy Board of Regents on October 24, 2006; final revision received on February 9, 2007.

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The Task Force on Research in Special Populations, commissioned by ACCP, was charged to review, update, and broaden the 1993 White Paper, *Women as Research Subjects*, to include other special populations. This paper, *Research in Women and Special Populations*, discusses important concepts regarding the conduct of research in these special populations and provides an expanded bibliography for readers interested in more detailed information.

Research in Children

It is well recognized that generalizing results from adult studies to the care of pediatric patients is dangerous, as infants and children are different from adults in many ways.² The maturational changes from the newborn period to adolescence results in a striking effect on drug disposition.³ For example, absorption,

distribution, metabolism, and excretion in neonates are different from adults because of age-specific changes in body composition, function, and/or age-specific patterns of development of phase I and II enzymes and renal function.⁴ Knowledge of these developmental changes has recently expanded greatly, resulting in a better understanding of the need for age-dependent drug therapy.⁴

Challenges in Pediatric Research

Inadequate Research Efforts

Until recently, little attention has been paid to the unique issues of medication use in pediatric patients. In fact, only 20% to 30% of drugs approved by the Food and Drug Administration (FDA) are currently labeled for pediatric use.² Drugs have historically only been evaluated in children after approval for use in adults, hence use of the phrase “therapeutic orphans” when referring to pediatric patients. This lack of testing is thought to be multifactorial, including a lack of financial incentive and the practical and ethical difficulties in conducting studies in children.²

Addressing Research Efforts in Children

Fortunately, recent regulatory and legislative changes have dramatically increased the number of pediatric drug studies. Congress enacted the Food and Drug Administration Modernization Act in 1997, which required the FDA to develop, prioritize, and publish a list of approved drugs for which additional pediatric information may provide health benefits for children.⁵ This act included a pediatric exclusivity provision that added 6 months of market exclusivity to any existing patent or exclusivity provided by the Hatch-Waxman Act for a drug for which the FDA requested pediatric studies and the manufacturer satisfactorily complied. In 1998, the FDA issued the Pediatric Rule.⁶ Under this regulation, the FDA could require that pediatric studies be conducted for a new drug that would likely be used in a substantial number of pediatric patients or would offer a significant benefit over existing treatments. The manufacturers of marketed drugs may also be required to do the same if either of these conditions applies and inadequate labeling could pose a significant risk.

The FDA in 2000 also published its Guidance for Industry regarding conducting clinical investigations in the pediatric population.⁷ In

2002, the Best Pharmaceutical for Children Act became law and continued the pediatric exclusivity incentive until 2007.⁸ For those drugs that are off-patent or that industry chooses not to conduct studies, the Best Pharmaceutical for Children Act mandates that the FDA and the National Institutes of Health (NIH) collaborate to assure the generation of pediatric data. The legality of this Act was challenged by the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert. Their claim was that the FDA did not have the legal authority to require pharmaceutical companies to conduct studies in the pediatric population. They voiced concerns that the pediatric exclusivity provision would increase the cost of new drug development, delay the availability of new drugs, and possibly cause the exploitation of children as research subjects. In 2003, the Pediatric Research Equity Act was passed that mimics the Pediatric Rule in requiring pediatric studies for certain applications and established a Pediatric Advisory Committee at the FDA.⁹

Ethical Issues of Pediatric Research

Historically, children have been exploited in medical research. A majority involved in early research were poor, institutionalized, mentally ill, or physically disabled.¹⁰ One early example was a study conducted to describe the natural history of hepatitis by deliberately infecting mentally retarded children institutionalized at the Willowbrook State School.¹⁰ Immunization trials for smallpox and pertussis also took advantage of children due to their lack of previous disease exposure and the controlled environment of pediatric institutions.¹⁰ Another more recent example conducted in the 1990s was a comparative study of the effectiveness of lead abatement procedures by the Kennedy Krieger Institute.¹⁰ This study was designed to determine a minimally effective procedure for lead abatement by comparison to the current standard. However, those receiving less than the standard abatement procedure were unnecessarily exposed to potential lead toxicity.¹⁰

Addressing Ethical Issues of Pediatric Research

In the 1970s, the National Research Act (Pub. L. 93-348) created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This group published

various reports, including the Belmont Report (which still serves as the basis of protection of human subjects in research) and the Children in Research report. Based on the National Commission's reports, the Department of Health and Human Services developed regulations for research, including Subpart A,¹¹ also called the Common Rule, and Subpart D, which provides additional protections for research enrolling children.¹² The National Commission acknowledged the need for research in children but also realized their vulnerability. To minimize these problems, they established strict criteria that research involving children should satisfy:¹³

- 1) the proposed research is scientifically sound and significant;
- 2) where appropriate, studies are conducted initially on animals and adult humans, followed by older children and then infants;
- 3) risks are minimized by using the safest procedures consistent with sound research principles and by using procedures needed for diagnostic or treatment purposes if possible;
- 4) adequate provisions are in place to maintain confidentiality of data and protect the privacy of children and their parents;
- 5) subjects are equitably recruited; and
- 6) adequate provisions for the permission of the parents or guardians and assent of the child are made.¹⁴

Further requirements included evaluation by the local institutional review board (IRB) to determine that the potential risk is: 1) justified by the anticipated benefit to the subjects, 2) the anticipated benefit:risk ratio is as favorable as with any alternative therapies, and 3) adequate permission of the parents or guardians and assent of the child is obtained. These guidelines both protected children from the risks of research and restricted their participation, especially the "children last" requirement. Institutional review boards are also required to categorize research involving children as: 1) research not involving greater than minimal risk, 2) research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects, 3) research involving no greater than a minor increase over minimal risk and presenting no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition, and 4) research with greater than a minor increase over minimal risk but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children. Research belonging to the last category requires approval by the IRB and Secretary of the

Department of Health and Human Services after consultation with a panel of experts.¹⁰

One of the current controversies is what constitutes "minimal risk" and a "minor increase over minimal risk." One point debated is whether minimal risk is relative to that experienced by healthy children in everyday life or by the children with the condition being studied. The National Commission defined minimal risk relative to the healthy child,¹³ while Subpart D in the federal regulations did not.¹² Another controversy is that according to the risk categories above, only children with a "disorder or condition" can be involved in nontherapeutic research that potentially has greater than minimal risk. Should healthy children be protected from risks preferentially to those with a disorder or condition? Perhaps it would be more ethical to either allow or prohibit such research for all children. Another recommendation has been proposed that instead of focusing on whether the child is healthy or has a disorder or condition, the definition of minimal risk should be risks and harms to which it would be appropriate to intentionally expose a child, as risks exposed to in the everyday life of a child may or may not be acceptable.¹⁵

Ideally, to determine age-appropriate dosage regimens for pediatric patients, pharmacokinetic studies enrolling children of all age groups would be conducted. One of the concepts currently being debated is whether healthy children should be allowed to participate in these nontherapeutic pharmacokinetic studies.¹⁶ The purpose for enrolling healthy children would be to isolate the effects of age and development on drug disposition. The risks involved typically include short-term exposure to the medication and the pain of serial blood sampling. In adults, this experience is considered minimal risk. However, blood sampling may be more traumatic in a child. The FDA has published guidelines¹⁷ reiterating the need for such studies and recommending techniques to decrease the risk to subjects (e.g., minimizing blood samples, minimizing blood volume per sample, etc.). Many arguments have been made for and against pharmacokinetic studies in healthy children. Arguments against include a lack of benefit for the subject, lack of true consent, that pharmacokinetics may be affected by disease state, investigator's potential financial gains influencing the need for subject accrual, studies with unnecessary "me too" drugs, and the school of thought that children do not have societal

obligations. Arguments for performing pharmacokinetic studies in healthy children include the fact that a medication may become relevant later if the healthy child becomes ill, availability of procedures to minimize risks (e.g., through the use of local anesthetics and a child-friendly environment), more expeditious generation of knowledge on age-dependent dosing in healthy children, lack of confounding variables to influence the study of age-dependent pharmacokinetics in healthy children, and the school of thought that children are an integral part of society and should be educated to help others.

The FDA provides some guidance on enrolling healthy children in drug trials. The Ethics Working Group of the FDA Pediatric Advisory Subcommittee stated, "In general, pediatric studies should be conducted in subjects who may benefit from participation in the trial. Usually, this implies the subject has or is susceptible to the disease under study. The Advisory Subcommittee utilized a broad definition of potential benefit. For example, any child has the potential to benefit from a treatment for otitis media." This statement makes it permissible to enroll healthy children in a drug trial for specific drugs targeted at specific conditions that commonly occur in pediatric patients. Therefore, it would be ethical if a patient of the appropriate age was enrolled in a study for a drug of clear importance to pediatric therapeutics in which the knowledge to be gained would be generalizable to the treatment of pediatric patients.¹⁶

Summary of Research in Children

In summary, pediatric drug research is a dilemma in that society wants to spare children from the potential risks of research but also from the inevitable harm of using inadequately studied medications.¹⁸ With the new policies implemented in the 1990s by the FDA, NIH, and Congress, some are concerned that too much focus has shifted from protecting children from research risks to ensuring access.¹⁴ Care must be taken to ensure that children are enrolled in research designed to provide pediatric-specific information and that study subjects receive at least standard of care.¹⁴

Research in the Elderly

The American population is aging, along with an increase in life expectancy.¹⁹ Currently, there

are 38 million seniors in the United States and, by 2030, that number will rise to 75 million.²⁰ The elderly population represents about 13% of the population and yet they consume about 34% of all prescription drugs,²⁰ probably due to a higher incidence of disease-related morbidities and therefore multiple medication regimens.²¹ Clinical pharmacy practice, research, education, and advocacy in older adults have been reviewed by a separate ACCP White Paper.²² This section of the current paper focuses on research issues in the elderly.

Given a longer life expectancy and the increased use of medications by the geriatric population, clinical research in the elderly becomes increasingly important. Besides the disproportionate increase in drug use, the elderly population has its particular research needs and gaps in knowledge that are distinct from other populations. Elderly individuals may respond to drugs differently than younger individuals. For example, altered pharmacokinetics and pharmacodynamics have been well documented in the elderly.²³ In addition, certain conditions such as Alzheimer disease and isolated systolic hypertension are prevalent predominantly in the geriatric population. Many drugs in use and in development by pharmaceutical companies are directed toward diseases affecting the elderly. In 2004, there were 800 new medicines targeted to diseases of aging by pharmaceutical companies, including 123 drugs in development for heart disease and stroke, 395 drugs for cancer, 53 drugs for diabetes, 22 drugs for Alzheimer disease, 18 drugs for osteoporosis, and 14 drugs for Parkinson disease.²⁴

Challenges in Geriatric Research

Inclusion of the Elderly in Research

Despite the fact that pharmaceutical companies are now required to include a geriatric use section in their product labeling, the information is often insufficient in part because insufficient numbers of elderly are included in the clinical trials.²¹ Effective lower doses of many drugs used in the elderly population are not included in product labeling. Cohen reported on 48 major medications where data are available on lower effective doses that is not reflected in the Physicians' Desk Reference (i.e., the product label).²⁵ Despite the importance of including older persons in clinical trials, underrepresentation of the elderly in research studies

has been well documented.^{26, 27} The lack of participation among the elderly in clinical trials adversely affects patient care ultimately. For example, in an analysis of adverse events reported to the FDA between 1990 and 1996, patients older than 60 years experienced 3 times more adverse events compared with individuals less than 20 years of age.²¹

A reason for lower participation by the elderly in research studies may be due to organ system abnormalities and functional status limitations as these individuals age. It has been estimated that if protocol exclusions for organ system abnormalities (e.g., cardiac function, blood pressure, hematologic, and pulmonary function) and functional status limitations were relaxed, the percentage of elderly participation in cancer trials would be almost 60%.²⁷ Due to the access barriers to research studies, elderly individuals who are recruited into and continue to be followed in clinical protocols usually are more independent, healthier, and have a higher cognitive function. This recruitment bias may make results in studies involving older individuals not generalizable. For example, patients with dementia included in clinical research are systematically younger than the general dementia patient population by a gap of about 8 years in mean age.²⁸ In addition, fewer than one-half of the older adults currently prescribed donepezil would have been eligible to participate in the randomized controlled trials that established efficacy of the drug.²⁹ In particular, discontinuation rates are higher among patient groups not represented in the trials.

In addition, recruitment and attrition may be particularly problematic in elderly individuals. Increased age brings greater inter-individual heterogeneity. Many confounders may also exist in older adults. Such confounders include residence, caregiver type, cognitive function, social support, lifestyle, health status, drug compliance, and health care access, to name a few.²² These inter-patient variability and confounders increase the sample size necessary in a given study. In addition, the drop-out rates may be higher in elderly individuals. Patients may become lost to follow-up because of relocation, change in health status, family influence, or a decline in cognitive function. The death rate in the elderly population is higher than that of younger populations, and this may be particularly an issue when the follow-up period for a study is long. There also exist

regulatory challenges in terms of recruitment. The Health Insurance Portability and Accountability Act (HIPAA) stipulates that authorization from the patient must be obtained before a researcher can collect the exact age of patients older than 89 years.

Addressing Elderly Participation in Research

The FDA published its first guidance document for industry regarding research in elderly individuals in 1989. In this Guidance for Industry, Guideline for the Study of Drugs Likely to be Used in the Elderly, recommendations mainly center on evaluation of age-related difference in pharmacokinetics because age-related pharmacokinetic differences have been documented more frequently than pharmacodynamic differences.³⁰ The FDA subsequently published another guidance document, Guideline for Industry Studies in Support of Special Populations: Geriatrics, in 1994.³¹ This subsequent document specifically stresses the importance of participation of elderly subjects in clinical trials evaluating drugs of clinical significance in the geriatric population. In addition, the guidance document states that arbitrary exclusion criteria based on an upper age limit should not be used and encourages the participation of individuals over 75 years of age.

As mentioned previously, relaxing protocol exclusions for organ system abnormalities in clinical studies can often result in increased elderly participation.²⁷ Given the inter-patient variability in this age group, sponsors' support would be paramount to expanding the inclusion of elderly individuals as research subjects.

As life expectancy increases, the exact definition of "elderly" may need to be revised. Most consider persons older than 65 years to be "elderly." However, as the population in their 70s, 80s, and 90s increase, research in these age subgroups may become important as well. In addition, measurement tools may need to be validated specifically in the elderly population. For example, in the Geriatric Depression Scale, questions regarding sexual interest and jobs outside the home are eliminated to reflect only items appropriate for older adults.

Cognitive Impairment

Another challenge in research involving older individuals is cognitive impairment and the informed consent process. Research issues in the cognitively impaired are discussed in Section 5.3.

Table 1. Major health disparities in ethnic/minority groups³⁶

Ethnic/minority group	Health disparities
African Americans	1. Infant death rates more than double that of whites; 2. Death rates from heart disease and cancer more than 40% and 30% higher than those of whites, respectively; 3. Death rates from HIV/AIDS more than 7 times that for whites; 4. A rate of homicide 6 times that for whites.
Hispanics	1. Are almost twice as likely to die from diabetes as are non-Hispanic whites; 2. Account for 20% of the new cases of tuberculosis; 3. Exhibit higher rates of high blood pressure and obesity than non-Hispanic whites.
Other ethnic/minority groups	1. American Indians and Alaskan Natives have an infant death rate almost double that for whites. 2. The rate of diabetes for this population group is more than twice that for whites. 3. American Indians and Alaska Natives also have disproportionately high death rates from unintentional injuries and suicide. 4. New cases of hepatitis and tuberculosis are higher in Asians and Pacific Islanders than in whites.

The Nuremberg Code states that volunteers participating in research should have “legal capacity to give consent.”³² Some older patients may be excluded from research studies because of cognitive impairment that renders such patients a “vulnerable population” that need protection from exploitation.

Addressing Cognitive Impairment in Elderly Research Subjects

The American Geriatrics Society states that older individuals should not be excluded from participating in research studies solely because of impaired cognitive function.³³ The American Geriatrics Society suggested conditions to be considered in the informed consent procedures by persons with cognitive impairment. Examples of these conditions include existence of advance directive for research, severity of cognitive impairment, existence of health care surrogates, whether the research is ethical and justified, and local laws pertaining to this area. In addition to difficulty in providing informed consent, cognitive function can pose challenges to elderly subjects’ ability to follow study protocol appropriately, comply with self-administration of study drugs, and report data accurately.

Summary of Research in the Elderly

As our population ages, inclusion of the elderly in research becomes increasingly important. Numerous physiological, social, and ethical barriers to including the elderly in clinical research exist. In addition, elderly participants of clinical trials are often more independent and may not be representative of elderly patients in whom the medication will be used.

Research in Ethnic/ Minority Groups

Although life expectancy and overall health have recently improved for most Americans, blacks or African Americans, Hispanics or Latinos, and Native Americans continue to experience disparities in the burden of illness and death. As these racial and ethnic minorities are expected to grow in proportion to the total United States population, the future health of America as a whole will be influenced substantially by the health of these groups.³⁴

The health disparities experienced by these groups compared with the white, non-Hispanic population in the United States have been identified to result from the complex interaction of genetic variations, environmental factors, and specific health behaviors in various clinical and social studies.³⁵ Table 1 summarizes the major health disparities experienced by African Americans, Hispanics, and other ethnic/minority groups.

Challenges in Research Involving Minorities

Genetic differences among ethnic/minority groups

It has been increasingly recognized that genetic difference among ethnic/minority groups is an important determinant in disease risk, progress, prognosis, and patient’s responses to treatment. African Americans have high rates of heart disease, including coronary artery disease, stroke, high blood pressure, and heart failure. A report from the American Heart Association indicates approximately 40% of African Americans have some form of heart disease in comparison to 25% of Caucasians.³⁷ A recent study has shown that African American women with coronary artery disease are twice as likely to have a heart attack than white women.³⁸ It has also been reported

that people of African, Hispanic, and Native American heritage are more prone to type 2 diabetes compared with their white counterparts.³⁹ More recent discoveries have shown that genes are potentially involved in the development of various diseases, such as Alzheimer disease, cystic fibrosis, cancer, hemophilia A, Huntington disease, hemochromatosis, fragile X mental retardation, familial adenomatous polyposis, and thalassemia. Although environmental triggers are necessary for ethnic minorities genetically predisposed to develop these conditions, this information has been or will be used in the prevention, early diagnosis, and treatment of these diseases.³⁵

Genetic differences or specific genetic factors found among ethnic/minority groups can affect the way people respond to certain medications. For example, the angiotensin-converting enzyme inhibitor, enalapril, reduces the rates of hospitalization in whites but not in blacks.⁴⁰ Furthermore, the β -blocker, carvedilol, is more effective than other agents in the same class in reducing the death rates or hospitalization in black patients.⁴¹ It has also been shown that self-declared black patients with severe heart failure appear to benefit from a combination of hydralazine and isosorbide dinitrate when added to background neurohormonal blockade,⁴² and retrospective analyses of heart failure trials suggest that black, but not white, patients have a clinically meaningful response to the isosorbide dinitrate/hydralazine combination.^{43, 44} In 2005, FDA granted approval for BiDil (hydralazine/isosorbide dinitrate) to treat heart failure in black patients, marking the first time that the FDA approved a drug for a specific racial group.⁴⁵

Instead of solely relying on epidemiologic information such as ethnic background, the focus of future studies would shift to individual genes that may influence drug response. As people of the same ethnic background may carry similar genes, studies based on race would provide pharmacogenetic information to some extent. An example is a classical study that evaluated the activity of thiopurine methyltransferase (TPMT) in patients receiving thiopurine drugs such as 6-mercaptopurine.⁴⁶ TPMT is an enzyme involved in the biotransformation of many drugs and xenobiotic compounds. The activity of this enzyme is present in the human red blood cell and is controlled by a common genetic polymorphism. Patients with inherited low levels of TPMT activity are at increased risk for thiopurine drug-induced myelotoxicity, whereas

subjects with high TPMT activities may be undertreated with these drugs. The genetic polymorphism of this enzyme shows distribution pattern varying with respect to ethnic background. Among Caucasians, 89–94% possess high enzyme activity with *TPMT*3A*, compared with low activity in Chinese and African Americans with *TPMT*3C*.⁴⁷

In recent years, the research on pharmacogenetic differences among ethnic minorities has broadened to include a larger range of targets such as multiple metabolizing enzymes, drug transporters, and receptors.⁴⁸ Increasing evidence suggests that drug metabolism alone does not account for the observed inter-racial variability in drug disposition or response but other processes, including drug transport, are important determinants of drug disposition. Among the drug transporters shown to play a key role in drug disposition, P-glycoprotein (P-gp) is one of the most extensively studied. The *MDR1* gene encodes P-gp, a drug efflux pump that decreases gastrointestinal uptake and intracellular concentrations of the antiretroviral protease inhibitors in HIV-infected patients. A recent report indicates that while patients with the homozygous CC genotype had higher plasma protease inhibitor levels when treated with these agents, immune responses significantly increased to a greater degree in patients with the TT genotype at the *MDR1* C3435T locus.⁴⁹ The wild type alleles of the *MDR1* gene (CC) are more prevalent in the African American population (75%) than in Caucasians and Hispanics (50%).⁵⁰ Such racial differences in the *MDR1* gene polymorphisms may contribute to previously recognized racial differences in the clinical response to protease inhibitors.

With a greater understanding of the genetic differences among ethnic/minority groups, it may be possible to select drugs and doses more precisely using compiled genetic information of a specific ethnic group or, possibly, individual patients. This could lead to more effective drug therapy, with greater safety and fewer adverse effects or treatment failures.

Enhancing Research in Genetic Differences Among Ethnic/Minority Groups

Research in genetic differences among ethnic/minority groups can be enhanced by the following:

- a. Expanding funding in the genetic research

infrastructure at institutions to increase the capacity to support ethnic/minority research and increase the number of funded investigators to improve outcomes in this research.

- b. Including racial and ethnic minorities in prevention, therapeutic, vaccine, and clinical trials in numbers that reflect the current incidence data and genetic background.
- c. Developing, evaluating, and sustaining effective interventions to prevent disease progress among racial and ethnic minorities with respect to genetic background.

Inclusion of Minorities in Research

The inclusion and retention of African Americans and other minority groups as clinical research subjects has become an important goal of contemporary clinical research practitioners. The relatively low participation rates of minority test subjects in clinical trials have slowed progress toward a comprehensive understanding of those emergent diseases that affect minority groups. For example, research has shown that although African Americans are over-represented in many chronic illnesses such as hypertension, diabetes, and cancer, studies of these diseases have often failed to attract and at times include enough African American participants to generate meaningful conclusions concerning these populations.

Within the literature, there is no universally accepted definition of the term "minority." It is a socially defined term, used to identify a group deemed to be occupying a nondominant status position. Minorities are distinguished by age, race, ethnicity, and/or cultural heritage. In American society, minorities include American Indian and Alaskan natives, Asian and Pacific Islanders, blacks, and Hispanics. Accompanying minority status is "vulnerability." Regulatory guidance documents such as DHHS regulation 45 CFR 46.111 (b)⁵¹ and FDA regulation 21 CFR 56.111⁵² list children, prisoners, pregnant women, handicapped, mentally disabled, educationally disadvantaged, ethnic minority groups, homeless, impoverished persons, and refugees as groups of persons who are "vulnerable." Vulnerable individuals are prone to coercion and exploitation and may participate in clinical trials as a means to obtaining medical care, thus exposing themselves to the risk of manipulation or undue influence from researchers.

Historically, minorities and impoverished persons have been prone to exploitation in clinical research. The Tuskegee experiment provides an example of how African American minorities were victimized and made vulnerable.⁵³ Impoverished persons, some of whom are minorities, suffer from discrimination; tend to have less access to education, social services, and health care; and are often behaviorally and politically stigmatized. An example of violations of an impoverished minority group occurred in the San Antonio Contraception study, which enrolled 76 impoverished Mexican-American women with previous multiple pregnancies. Without their knowledge, Mexican-American women who sought oral contraceptives at a clinic were placed in a 2-way, crossover study. In the first phase, one group was given a placebo and the other an oral contraceptive. In the second phase, women initially placed on placebo received oral contraceptive and those initially receiving oral contraceptives were crossed over to placebo. Eleven women became pregnant during the study, 10 while using placebo.⁵⁴ These impoverished women sought preventative medical care but were exploited by the existing clinical program. Research occurred without their consent and the risks clearly outweighed any benefit.

In 1990, the NIH established one of the first policies requiring the mandatory inclusion of women and other minorities in clinical research.^{55, 56} Despite this policy, minorities were poorly represented in clinical trials because issues barring their participation were quite different than that of women. With minorities, the legacy of the Tuskegee study and mistrust of the medical profession were paramount. These guidelines had been developed but did not require the reporting or analysis of the data regarding race or gender, making it impossible to establish the success of these mandates in attracting and retaining women and minorities. In 1994, after reports indicated that these policies were not being uniformly adhered to, the NIH along with the Office of Research on Women's Health (ORWH) and the NIH office of Minority Health joined forces and issued revised guidelines on the necessity of inclusion of women and minorities in clinical research and emphasized the reporting of analysis of sex and race/ethnicity differences in research results in NIH phase 3 clinical trials.⁵⁵ Inclusion of the results of subset

analyses was strongly encouraged in all publication submissions. If the analysis revealed no subset differences, a brief statement to that effect, indicating the subsets analyzed, would suffice.⁵⁷

The barriers to increasing minorities' participation in clinical studies are diverse. Mistrust and fear of being "guinea pigs" have been cited by minority subjects as the major reason for not participating in research studies.⁵⁸ In some instances, barriers to their participation in clinical trials reside within organizational structures.⁵⁹ Organizational barriers exist where there is a lack of racial diversity in the research team or organization. It has been suggested that if the race of the recruiter and the target group are discordant there is even greater challenge.⁶⁰ The same is true when recruiters are viewed as outsiders to the community they wish to study.⁶¹ Basic considerations such as the hours of operation of a facility may adversely impact potential subjects' ability to participate. Minorities or impoverished persons are more likely to have hourly paid jobs and, as such, time away from work for research participation negatively impacts their income.

In addition, bureaucratic processes such as penalizing illegal aliens may deny them from participating in clinical trials even though they live, work, and sometimes die in America. As the United States population becomes more diversified, researchers must be cognizant of the impact of laws and a lack of English proficiency of potential minority subjects⁶² on attracting and retaining potential subjects.

Barriers to minority participation in clinical trials can also be resource related. Such barriers occur when there are limited resources available to provide the services needed to meet the needs of the target group. This may include the expense required to make culturally relevant brochures, advertisements, cost of translation services, or staff education. In some cases, the incurred costs of participating are not offset by remuneration received from participating in clinical trials.

Addressing Barriers to Minority Research Participation

In order to improve the health status of underserved populations, including racial and ethnic minorities, several agencies have been created, including the Office of Minority Health in the U.S. Department of Health and Human

Services (1985) and the Centers for Disease Control and Prevention (1988). The Disadvantaged Minority Health Act was passed by Congress in 1990.⁶³ More recently, the initiatives Healthy People 2010 and Racial and Ethnic Approaches to Community Health (REACH) 2010 have been launched to increase quality and years of healthy life and eliminate health disparities. In particular, Racial and Ethnic Approaches to Community Health (REACH) 2010 is designed to eliminate disparities in six priority areas in which racial and ethnic minorities experience serious disparities in health access and outcomes, including infant mortality, deficits in breast and cervical cancer screening and management, cardiovascular diseases, diabetes, HIV infections/AIDS, and child and adult immunizations.⁶⁴ In addition, Healthy People 2010 reinforced the need to include enough individuals from different segments of the population in clinical trials.⁶⁵ Part of the Healthy People 2010 initiative is to gain comprehensive understanding about diseases that affect minority groups. To achieve this objective, clinical trials must be based on populations that are large enough to eliminate statistical bias.

It has been suggested that the structural, organizational, and economic barriers for recruitment and retention of minorities and impoverished subjects can be achieved through comprehensive planning that considers structural and individual influences negating minority group participation in clinical trials.^{59, 66} Among the more important issues to be addressed include the following:

- a. Building trust within minority communities through communication about the need for their participation and making participants fully cognizant of their rights as clinical test subjects.
- b. Ensuring cultural competency of all clinical researchers.
- c. Building diversity among the student population of clinical researchers who are enrolling in relevant college programs of study. In keeping with this thrust to an integrative approach, the Accreditation Council for Pharmacy Education adopted revised Doctor of Pharmacy education standards that included diversity and cultural competency.⁶⁷ These standards were released in February 17, 2006 and will become effective July 1, 2007.

d.Ensuring due vigilance in reporting participation rates of clinical research test subjects and analysis of these data with regards to race and gender, such as that required of federally funded programs.

In addition to the above, further outreach approaches on the recruitment and retention of minority research subjects can be found in *Outreach Notebook for the Inclusion, Recruitment and Retention of Women and Minorities in Clinical Research*, published by ORWH.⁶⁸

Summary of Research in Minorities

Numerous barriers exist for including minorities in clinical research. These barriers include language difficulties, financial barriers, mistrust by minority subjects, and researchers' lack of cultural competency. Although federal regulations and guidances encourage the inclusion of minorities in clinical research, improvement of minority participation in research need to be addressed via communities, among clinical researchers, and within education institutions.

Research in Vulnerable Populations

Prisoners, refugees, and the mentally ill are considered to be vulnerable populations for whom measures of protection from possible exploitation and harm need to be taken. There is considerable debate surrounding the use of these persons for clinical research. The principle of "respect for persons" would require that these individuals not be deprived of the opportunity for involvement in research. However, under conditions of incompetence or the institutional setting, protection from coercion or undue influence must be afforded.⁶⁹

Refugee Populations

A refugee has been defined as "a person who is outside his/her country of nationality or habitual residence; has a well-founded fear of persecution because of his/her race, religion, nationality, membership in a particular social group or political opinion; and is unable or unwilling to avail himself/herself of the protection of that country, or to return there, for fear of persecution."⁷⁰ Internally displaced people (IDPs) are similar, but still live within the borders of their home country. Refugees are considered to be vulnerable for many reasons. If

they are non-citizens of the country in which they are residing, they may not be afforded the same legal rights and regulatory protections of the host country. The United Nations Convention on Refugees in 1951 and the subsequent Protocol in 1967 provided guidance regarding the treatment of refugee populations to include travel documents, unification of families, welfare services, freedom of religion, access to courts, and employment.⁷⁰ Host countries can use their own judgment in the application of domestic law to these people. Political upheaval and social destruction are often inherent in the creation of a refugee population. Refugees are the victims of hostility by those who drove them from their home country and may not be entirely welcomed by the citizens of the country to which they fled. Authorities may do little to ensure that ethical conduct of clinical research is maintained in the refugee population.⁷¹ The vast majority of internally displaced peoples are women, children, the elderly, and the disabled. Because IDPs are living within their own country, there is no international agency to protect them; it is assumed that their own government will bear that responsibility. Often, people are transplanted within their own country due to internal conflicts that cause one of the factions to be favored to other factions. Due to this, IDPs are not protected or cared for because of prejudice.⁷²

The issue of conducting research in refugee populations is not specifically addressed or mentioned in international regulations that provide direction to those involved in clinical research. This includes the Belmont report, the Nuremberg Code, the Declaration of Helsinki, and the Council for International Organizations of Medical Sciences.^{32, 69, 71} Emergency relief personnel may work under conditions in which the interventions provided may lack proven scientific efficacy. There is a need to establish evidence-based emergency practices while protecting the refugee and internally displaced populations from possible exploitation or harm.⁷³

Challenges in Research Involving Refugees

There are numerous barriers to ethical clinical research using refugees and internally displaced people as subjects. They are economically impoverished and may be easily influenced to participate in research that they may believe will bring them financial gain, improvements in living conditions, or the semblance of cooperation with

authorities. Effective communication with these persons may be complex due to obstacles created by differing languages and cultural norms. Refugee and IDP populations may be appealing to researchers because of the “captive audience” that they represent. Refugees may be placed in “camps” that will limit their movement and be consistent in population. Follow-up studies may be easier to design and implement.⁷¹ Researchers must consider the psychological and social stressors experienced by refugees that may contribute to varying degrees of mental status changes. Voluntary informed consent of the type that would be expected in other areas of clinical research may be extremely difficult to obtain from this group of subjects. The question of whether consent given in crisis situations meets the test of being freely given must be answered.

The ethical requirements for studies involving this population must be higher than those needed for a less vulnerable population. Refugees participating in clinical research may not receive significant benefit from the study, but may incur risks. Humanitarian researchers believe that studies evaluating the extreme problems experienced by this population will improve knowledge that will benefit future people in crisis situations.⁷³ Guidelines for research in refugee and IDP populations have been proposed and include the following⁷³:

- a. Undertake only those studies that are urgent and vital to the health and welfare of the study population.
- b. Restrict studies to those questions that cannot be addressed in any other context.
- c. Restrict studies to those that would provide important direct benefit to the individuals recruited to the study or to the population from which the individuals come.
- d. Ensure the study design imposes the absolute minimum of additional risk.
- e. Select study participants on the basis of scientific principles without bias introduced by issues of accessibility, cost, or malleability.
- f. Establish the highest standards for obtaining informed consent from all individual study participants and, where necessary and culturally appropriate, from heads of household and community leaders (but this consent cannot substitute for the individual consent).
- g. Institute procedures to assess, minimize, and monitor the risks to safety and confidentiality for individual subjects, their community, and

their future security.

- h. Promote the well-being, dignity, and autonomy of all study participants in all phases of the research study.

Prisoner Populations

Prisoners who may be recruited to participate in clinical research are considered vulnerable research subjects for many of the same reasons as refugees and the internally displaced. As opposed to the refugee population, regulatory guidance does exist to aid researchers in developing research protocols that acknowledge these vulnerabilities. The Ethical Principles and Guidelines for the Protection of Human Subjects of Research, or The Belmont Report, defined and summarized basic ethical principles pertaining to general clinical research.⁶⁹

Challenges in Research Involving Prisoners

Socially, prisoners are deprived of many freedoms and are controlled by the environment in which they live. They rely on the prison system for basic needs that include shelter, food, and clothing. A prisoner may believe that he may receive an improved living condition, extra privileges, or a shortened prison sentence secondary to his participation as a research subject. The prisoner may not be able to make sound judgments with respect to voluntary informed consent to participate in a study because of his perceived need to please those in power or receive increased entertainment or exercise time. A prisoner may simply be bored with the regimented life in a prison. Participation as a research subject may relieve boredom or allow the prisoner the opportunity to distinguish himself from other inmates.⁷¹

The prison population is appealing to researchers for many of the same reasons as the refugee population. Depending on the length of the prison sentence, prisoners will be living in the same place with the same environmental and social conditions throughout the length of the study. Follow-up studies would be less complex to implement in this population. Unfortunately, there is evidence of researchers conducting risky research in this population due to the perception of a reduced societal “value” of prisoners relative to non-incarcerated individuals.⁷¹

Title 45CFR46, Subpart C, of the U.S. Code of Federal Regulations, entitled Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as

Subjects, was enacted by the Department of Health and Human Services (DHHS) in 1978 to address many concerns relative to conducting research in the prisoner population.⁷⁴ These regulations are applicable to all biomedical and behavioral research that is conducted or supported by the DHHS. Subpart C provides safeguards to prisoners to ensure that a voluntary and uncoerced informed consent is given for participation in clinical research. The membership of the IRB that reviews and approves research protocols in the prisoner population must include a prisoner member or a prisoner representative with appropriate background. Assurances are provided that parole boards will not be aware of a prisoner's participation in a study and that the prisoner is informed of this provision.⁷⁴

Title 45CFR46, Subpart C also defines permitted research in the prisoner population. Proposed research must only include the following⁷⁴:

- Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
- Study of prisons as institutional structures or of prisoners as incarcerated persons.
- Research on conditions particularly affecting prisoners as a class; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults provided that they study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.
- Except as provided above, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

The “Mentally Ill” or “Decisionally Impaired”

An accurate term to describe individuals with diminished mental capacity who do not have the consistent ability to provide voluntary informed consent for participation in clinical research

studies cannot be found in the guidelines and recommendations put forth by consensus experts and advisory committees. “Mentally ill,” “decisionally impaired,” “mentally incompetent,” and “cognitively impaired” are all descriptors that have been used.^{71, 75–77} Although controversy exists as to how to define these individuals, there is agreement that, while persons who are mentally ill are a vulnerable research population, they may be able to be autonomous in participating in clinical research. A statement published by the NIH acknowledged that impaired cognitive ability is not restricted to persons with neurologic, psychiatric, or substance abuse problems, nor should it be assumed that persons with these disorders have questionable capacity.⁷⁵

Challenges in Research Involving Persons with Cognitive Impairment

Disease states that are associated with cognitive impairment include dementia, delirium, schizophrenia, bipolar disorder, and depression. Persons suffering from schizophrenia, bipolar disorder, and depression will have fluctuating courses of illness that may produce periods of impaired capacity to understand the risks and benefits of involvement in research. Even when it is perceived that the subject is able to provide informed consent, it may be difficult for him/her to anticipate the consequences relative to future recurrences of illness.⁷⁸ Individuals diagnosed with dementia can be expected to follow a prolonged, consistent decline in cognitive functioning that will continue to impact decision-making abilities. Substance abuse disorders can result in states of intoxication similar to delirium and reduce cognition and attention.⁷⁸

The mentally ill are often stigmatized in many settings by those who assume they are dangerous, impaired, and unable to provide any care for themselves.⁷⁶ This compounds the social isolation experienced by persons with severe mental illness who may already feel inadequate. Mentally incompetent individuals may be prone to influence by those close to them such as caregivers or individuals involved in their treatment. They may consent to involvement in clinical research in an attempt to be cooperative or gain acceptance.⁷¹ Living in an institutionalized environment creates concerns similar to those of the prison population, where the belief may be that participating in a study

may allow for special privileges. The consequences of mental illness for those able to live in community settings can be staggering. Unemployment, substance abuse, disability, homelessness, and incarceration are common, contributing to an increased vulnerability in this population.⁷⁹ Persons with severe mental illness are often considered to be nonadherent to treatment recommendations, including missing appointments, refusing to follow up on referrals, and noncompliance with medication treatment regimens.⁸⁰ Due to these problems, many individuals will be continually hospitalized, both acutely and chronically.

The “deinstitutionalization” of the mentally ill began in the mid-1980s in the United States.⁸⁰ Those who were deemed capable of residing in the community were released to group homes, apartments, and shelters. The availability of supervised or structured housing was limited in many areas and the burden on the community mental health centers to provide care was strained. As a result, the number of mentally ill homeless soared and, with it, an increase in comorbid substance abuse and incarcerated persons. Today, jails and prisons can be considered “holding areas” for the mentally ill. It is estimated that approximately 16% of those in state prison facilities have been diagnosed with a mental illness.⁸⁰

Addressing Barriers to Research Participation by Mentally Incompetent Individuals

It is well recognized that research relative to both the underlying pathophysiological processes of psychiatric disorders and the development of new treatments for the illnesses is of paramount importance. It is estimated that 5 to 10 million adults in the United States suffer from severe mental illness and that the annual cost of untreated mental illness is more than \$100 billion.⁷⁹ It is not a question of whether to engage in clinical research in the mentally ill, but how to ensure that study subjects who may be cognitively impaired are protected from unethical or victimizing research.

The practice of excluding the mentally incompetent from research studies would solve the ethical dilemmas with respect to informed consent and the Nuremberg Code, but would cease advancement of knowledge in the understanding of the physiologic deficits of mental illness and the creation of more effective treatment options. In order to avoid subjecting

those with mental illness to unnecessary involvement in research, it has been suggested to limit research to studies that are relevant to the conditions prevalent in the decisionally impaired.⁷⁸ Advocacy groups such as the National Alliance for the Mentally Ill support research in severe mental illness, insofar as it is consistent with the highest scientific and ethical standards for protection of research subjects.⁷⁹

The NIH recommend several “points to consider” when developing research involving persons with a questionable capacity to consent.⁷⁵ The first is to avoid potential conflicts of interest. Often, the researchers who are recruiting these individuals are clinicians who are also providing care and it may be difficult for the mentally impaired person to differentiate between research and treatment, leading to confusion for the potential participant. Therefore, it is important that the consent process indicate differences between clinician and investigator and between treatment and research. The IRB should include a member who is experienced in working with people with mental illness or a member from an advocacy group. The capacity to consent to participation must be assessed by the investigator, including the individual’s understanding of the risks, benefits, and alternatives to participation in the study. The consent process will require ongoing assessment due to fluctuations in the decision-making capacity of the individual. Safeguards should be put in place within the study protocol to account for increases in decisional impairment as the study progresses. The study participant should be reeducated about the study protocol at frequent intervals to assure continued understanding and to provide assessment of cognitive stability. The IRB is advised to appoint an independent monitor to be present when the study investigators interview potential study candidates and/or their caregivers to ensure ethical conduct of research when the study involves greater than minimal risk.⁷⁵

The use of proxy consent was first adopted in the formulation of the Declaration of Helsinki in 1964 as an alternative for those study participants unable to give direct informed consent.⁷¹ The most recognized source for proxy is consent given by one who is legally authorized to do so. A question arises concerning what kind of clinical research is appropriate for proxy consent. Therapeutic research involves direct benefits to the participant, while nontherapeutic research does not. It is generally accepted that

nontherapeutic research can be performed using normal subjects and is, therefore, not appropriate for mentally incompetent individuals. There is concern that use of proxy consent does not adequately protect from exploitative research. Because of this, the NIH suggests that, along with proxy or surrogate consent, the assent of the individual study participant be obtained. The autonomy of the individual should be respected, as well as the right of that individual to withdraw from the study at any time.

An advance directive to participate in research that is executed at a time that the mentally incompetent individual is competent to consent may be considered where the law permits.⁷⁵ Another safeguard that may be implemented by the study investigator is a waiting period. Those who are cognitively impaired may need more time to consider the educational information that they are given regarding the study protocol or they may want to consult with family members or trusted caregivers. Information should be provided in small increments over time to allow for improved comprehension by the individual and the greatest likelihood of voluntary informed consent.⁷⁵

The World Medical Association (WMA) adopted a policy statement on ethical issues concerning patients with mental illness in 1995.⁸¹ In it, the WMA states that “the discrimination associated with psychiatry and the mentally ill should be eradicated; this stigma often discourages people in need from seeking psychiatric help, thus aggravating their situation.”⁸¹ The inability of the mentally ill patient to exercise autonomy or provide informed consent does not differ from any other legally incompetent patient. The person diagnosed with a mental illness should not automatically be assumed to be legally incompetent and his/her judgment should be respected.⁸¹ The statements of this world body provide the foundation upon which to build ethical and appropriate standards for the conduct on clinical research studies in the mentally ill.

Summary of Research in Vulnerable Populations

Numerous barriers and challenges exist in conducting research in vulnerable populations. Refugees and prisoners are appealing to researchers because of the “captive audience” that they represent. Guidelines for research in refugee and internally displaced populations have been proposed to protect these vulnerable

populations from possible exploitation or harm. Similarly, federal regulations were also enacted to protect prisoners participating in biomedical and behavioral research. Mentally ill and decisionally impaired persons constitute another group of vulnerable research subjects. It is recognized that clinical research in subjects with mental illness or dementia is of paramount importance, as the advancement of understanding of these disorders will encourage development of new treatments for these disorders. Recommendations have been put forth by the NIH and WMA for protecting mentally ill and cognitively impaired persons in clinical research.

Research in Women

Sex-related Variability in Pharmacokinetics and Pharmacodynamics

Over the last few decades, it has become increasingly evident that there are sex-related differences in pharmacokinetics and pharmacodynamics.^{82, 83} Pharmacokinetics studies focus on the relationship between drug dosage and concentration of drug over time in blood or plasma and preferably in cells and tissues, which may better represent the site(s) of action.⁸⁴ Sex-based differences in bioavailability, distribution, metabolism, and elimination exist that contribute to variability in drug response. Bioavailability of oral agents appears to be higher in women than men, while transdermal drug administration does not seem to be affected by sex.⁸⁵ Gastric emptying time is slower in women than men, primarily due to the effects of estrogen and transit time may vary throughout pregnancy and the menstrual cycle.⁸⁴

Since body composition, plasma volume, and plasma protein binding vary between women and men, it follows that the rate and extent of distribution may vary. Women have higher body fat, lower average body weight, and smaller average plasma volume than men. Therefore, lipophilic drugs (such as benzodiazepines and neuromuscular blockers) have increased distribution volumes in women.^{84, 85} Albumin concentrations do not consistently vary by sex, but exogenous estrogens can increase the levels of serum-binding globulins and may impact sex hormone-binding globulin, corticosteroid-binding globulin, and thyroxine-binding globulin in women.⁸⁴ Many believe the most important factor in adjusting medication dosages between women and men may be adjusting for body size,

especially for loading doses or drugs with a narrow therapeutic window.^{86, 87} Overall, the extent of clinical differences in distribution has not yet been precisely defined.

Of all pharmacokinetic parameters, drug metabolism seems to play the greatest role in variability between women and men. Sex-based differences exist in both phase I (oxidation, reduction, and hydrolysis mediated through the cytochrome [CYP] P₄₅₀ system) and phase II (glucuronidation, sulfation, acetylation, methylation, or glutathione conjugation of the parent drug or its phase I metabolite) reactions. A classic example of a phase I reaction difference between women and men is shown with drugs metabolized by the isozyme, CYP3A4. Agents such as erythromycin, midazolam, and verapamil are typically metabolized and cleared faster in women. Reasons for this difference are thought to be a variance in CYP content or activity.⁸⁴ Although most phase II reactions are primarily due to racial and genetic differences, some data on sex differences exist. A comprehensive discussion of these reactions can be found elsewhere.⁸⁵ Conflicting data exist on whether menstrual cycles, menopausal status, or estrogen and progesterone levels in hormone therapy significantly affect drug metabolism in women.⁸⁴ In addition, sex-related factors, such as use of hormonal contraceptives, may affect drug metabolizing enzymes.⁸²

Drug excretion is usually mediated by the kidney or liver. Glomerular filtration, because it is directly proportional to weight, is higher on average in men than women. This reinforces the importance of sex-adjusted dosage selection for renally excreted drugs with narrow therapeutics windows and/or adverse effects related to concentrations.⁸⁵ Further study on sex-based differences in renal excretion is warranted to clearly explain the contribution of this factor.

Pharmacodynamic and behavioral differences between men and women have been well documented. A pharmacodynamic difference exists when similar plasma concentrations of a drug in the two sexes do not produce the same pharmacologic outcomes. Numerous examples in pharmacodynamic differences exist. It is also well documented that women experience drug-related adverse events more frequently than their male counterparts.⁸⁸⁻⁹⁰ For example, multiple studies have shown that women seem to have more frequent and severe side effects with protease inhibitors and nucleoside reverse transcriptase inhibitors than men.⁹¹⁻⁹⁶ Women

tend to demonstrate greater analgesic effects with opioid agonists compared with men.⁹⁷⁻¹⁰⁰ In clinical trials, women have not always experienced the same benefits as men, especially with regards to cardiovascular outcomes.^{101, 102} Negative consequences may result with differences between women and men for delay in presentation and treatment with coronary heart disease.¹⁰³ Women also appear to score lower than men on measures of health status and functioning in diabetes.^{104, 105} Despite several examples of these pharmacodynamic and behavioral differences between women and men, little is known about the direct interplay of pharmacokinetics and especially genetics with these factors.

Sex-related Genetic Differences

The distinct role of genetics in sex-based differences is much less clear than pharmacokinetics. Findings of differences at the biochemical and cellular level, specifically at the XY (male) and XX (female) sex chromosome level, are beginning to more clearly define how women and men may express individual drug variations.

In 2001, the Committee on Understanding the Biology of Sex and Gender Differences, Institute of Medicine published, *Exploring the Biological Contributions to Human Health: Does Sex matter?*⁸⁷ The report explored sex differences and determinants of these differences at the biological level. There are several mechanisms for the genetic basis of sex differences:

1. Genes on the Y chromosome are expressed only in males, with many having no counterpart on the X chromosome; therefore, expression of Y genes will be limited to males.
2. Some genes on the X chromosome are expressed at higher levels in females than in males. Although there is a process of inactivation of one of the two X chromosomes in females to attempt to equalize the "effective dosage" of the X chromosome, not all genes on the inactivated X chromosome respond to this process. The relatively few genes not equalized can have significant impact on the phenotypes of cells.
3. The expression of many genes is likely to be influenced by hormones. Therefore, some genes may have limited expression in sexually dimorphic tissues or cell types (e.g., the ovary, breast, testis, and prostate).

At this point, only a limited number of genes have been examined for sexual dimorphism. However, some data are known about possible effects between the sexes of any variant in an X-chromosome-linked gene. For example, mosaicism occurs in females where the two X chromosomes express the alleles of the paternally inherited X chromosome and maternally inherited X chromosome, respectively. Therefore, expression of an X-chromosome-linked phenotype is often much more variable in females than in males. With hemizyosity, males have only one X chromosome and functional variants cannot be “masked” by a second X chromosome. Thus, males often demonstrate a more common, clear, or extreme version of the variant phenotypes than females. Scientific discovery of differences in expression through the female and male genome should produce fascinating findings.

The issue of whether there are differences in the biochemistry between female and male cells has also been explored. There is a potential for 1

in 20 biochemical reactions to differentially affect male versus female cells because the sex chromosomes comprise approximately 5% of the total human genome.⁸⁷ With this knowledge, it is possible to imagine that male and female cells will differ in at least some aspects of basic biochemistry, especially given the complexity of most biological pathways. Table 2 displays the genetic factors that may differentially affect the basic biochemistry of male and female cells.

Genomic imprinting is the concept that some genes are expressed only from the maternal allele and that others are expressed only from the paternal allele.⁸⁷ This concept reinforces the acknowledgment that there are multiple biochemical differences between the gametogenic cells of males and females and that these differences may affect the expression of genetic information in the next generation. For example, since males have only one maternal X chromosome and female have both a maternal and paternal X chromosome, X-chromosome-linked genes that pass through the paternal line

Table 2. Progression of public guidelines regarding women in clinical research

Year	Event
1986:	NIH established New Policy on Women's Health Research to increase participation in women's health research
1988:	FDA issued Guideline for the Format and content of the Clinical and Statistical Sections of New Drug Applications. This guideline emphasized the necessity of including demographic data and their analyses in NDA applications.
1990:	Institute of Medicine Report stated that NIH was not adequately implementing its 1986 policy to increase participation in women's health research.
1990:	General Accounting Office study revealed that implementation of NIH's 1986 policy was slow and gender analysis was not implemented. This subsequently led to media and public reaction.
1990:	Office of Research on Women's Health was established at the NIH to simulate and serve as a central point for women's health research. A scientific workshop and public hearings were held at Hunt Valley, Maryland. These series of scientific meetings produced the report “The National Institutes of Health: Opportunities for Research on Women's Health.” The Hunt Valley report served as a guide for women's health research at the NIH.
1993	NIH Revitalization Act was enacted by Congress. This law requires the inclusion of women and members of racial and ethnic minority groups in all federally-funded research studies.
1993	FDA issued “Guidance for Industry. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs.” Under this new guidance, pharmaceutical sponsors were required to include a full range of patients in their clinical studies, and to carry out analysis to evaluate differences in subsets of patients. The guidance also emphasized that women should be included in <i>all</i> phases of clinical drug development. Women and minorities must be included in phase III clinical trials in <i>numbers adequate</i> to allow for valid analyses of differences in intervention effect. Cost is not allowed as an acceptable reason for excluding these groups.
1994	Offices of Women's Health were established at the FDA and Centers for Disease Control and Prevention
1994	FDA issued guidance lifting the ban (in place since 1977) barring the inclusion of women with childbearing potential from Phase 1 and early Phase 2 clinical studies. This ban had been a significant barrier to women's participation in clinical trials.
1997:	FDA issued “Proposed Rule on Investigational New Drug Applications: Proposed Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases.” This rule allowed the FDA to put protocols under an IND on clinical hold if a pharmaceutical sponsor proposed exclusion of women or men with reproductive potential.
1997:	The Office of Women's Health Research published “An Agenda for Research on Women's Health in the 21st Century.” These series of documents expanded the Hunt Valley vision for women's health research.

Table 3. Genetic factors that may differentially affect the basic biochemistry of male and female cells.⁸⁷

Gender	Genetic factors
Male	X-chromosome-linked recessive mutations Expression of Y-chromosome-specific genes Changes in androgen-responsive genes in germ-line or somatic cells
Female	Expression of some genes from both X chromosomes Defect in initiation or maintenance of X-chromosome inactivation Changes in estrogen-responsive genes (e.g., the HER2 gene in breast cancer) in germ-line or somatic cells

have the potential to affect female offspring, but not male offspring. These findings may have more significant clinical implications when applied to behavior or cognitive function in males and females. In addition, recent evidence of differential timing in the establishment of maternal and paternal methylation imprints serve as an example of the sexual dimorphism of imprinted gene expression.¹⁰⁶

Last, the male produces billions of sperms from a population of stem cells that continue to divide throughout the entire adult life and the female produces a relatively small number of ova (approximately 500) from a limited number of oocytes that form in embryogenesis. This numerical difference indicates that most mutations resulting from DNA replication errors take place in the male germ line. However, the magnitude of this difference and the clinical significance has yet to be determined.

Males and females have partially different genomes. The findings discussed here indicate that there are multiple differences in the genetic information, biochemistry, and pharmacokinetics of males and females that can affect an individual's health and drug response. What we have learned is that many of these differences do not arise solely because of the hormonal environment. Further research in sex-based differences regarding pharmacokinetics and genetics is warranted and important to further our understanding of the human condition.

In summary, sex-related variability and genetic-based sex differences in drug response makes it necessary to include women as research subjects in clinical studies. Despite this fact, women have been historically under-represented in clinical trials.^{107, 108}

Challenges in Inclusion of Women in Research

The ethical and social considerations of including women in research have been extensively discussed.^{109, 110} The current concern regarding participation of women in clinical studies arises from conflicting public policy positions: protectionism and access. The need for research subject's protection was emphasized in the 1950s and 1960s in response to unethical research conduct. The discovery of adverse outcomes in children who had fetal exposure to certain drugs during pregnancy further reinforced the protectionism emphasis. In the mid-1970s, legislation was passed to protect research subjects from unethical treatment. The regulations resulting from this legislation also were designed to protect against fetal injury by restricting the inclusion of women of childbearing potential and pregnant women and in drug trials. However, women-specific conditions and sexual dimorphism in drug response made researchers recognize the need to recruit women subjects in drug studies. Over the past two decades, the NIH and FDA have switched from a protectionistic to an inclusive policy regarding women participating in clinical trials (Table 3).

Despite these regulatory shifts in public policies to a more inclusive agenda to encourage women participation in clinical studies, recent analyses still show an alarming under-representation in women participants in phase 1, 2, and 3 clinical trials.^{110, 111} In an analyses of four high-impact journals, Vidaver et al found that 20% of phase 3 clinical trials excluded women, and only up to 25% of articles included an analysis of results specific to gender differences.¹¹¹

Reasons for a lack of women participation in clinical studies are multifactorial. Inclusion and exclusion criteria, especially in the field of cardiovascular medicine, may favor inclusion of men.¹¹⁰ Women are usually older and therefore have more comorbidities when they experience their first myocardial infarction. These comorbidities may render them less likely to participate in clinical trials. It has also been documented that women are less likely to provide informed consent,¹¹² and male physicians are less likely to enroll female than male patients into clinical studies.¹¹³ In addition, phase I studies and studies in healthy volunteers have a higher rate of excluding female participants,¹¹⁰ suggesting that some investigators may still consider it unethical to expose women of childbearing potential to a drug without any benefit other than a small financial gain.

Addressing Challenges in Inclusion of Women in Research

The appropriate inclusion and representation of women and minorities in biomedical research and clinical trials is an explicit criterion evaluated during reviews of such proposals for NIH funding.¹¹⁴ This criterion also applies to research conducted at NIH-funded General Clinical Research Center units at local institutions. These provide principal investigators incentives to ensure recruitment of balanced and representative mix of gender and minority groups into their research projects.

In addition, the OWRH has published an Outreach Notebook for the Inclusion, Recruitment and Retention of Women and Minorities in Clinical Research.⁶⁸ Some strategies that may aid the recruitment and retention of women in clinical research include the following:

- a. Involving the community: For example, the support and collaboration of women community physicians who provide care for the targeted population can be solicited.
- b. Involving the participants: For example, women participants should be included in the design of the research and preparation of study materials to be sure they meet their needs. In addition, women respond positively to messages of altruism that convey the benefits of research to future generations.
- c. Staffing of the research team: For example, women investigators and staff may foster greater trust among female participants.

- d. Addressing logistical and financial need: For example, offering childcare, maintaining extended and flexible clinical hours, and other financial incentives may offset some inconveniences due to research participation.
- e. Improving communication: Allowing extra time to review study procedures and benefits, questions and answers, for participants with special needs (e.g., parents with young children).

Summary of Research in Women

Sex-based variations in pharmacokinetics and pharmacodynamics have become increasingly evident. In addition, genetics may play a role in defining how men and women respond differently to medications. Sex-based variability in drug response makes it necessary to include women as research subjects in clinical studies. Historically, women were under-represented in clinical trials, in part because they were "protected" from participation due to a concern of fetal exposure to drugs. Over the past two decades, the NIH and FDA have switched to an inclusive policy, encouraging inclusion of women in clinical studies. However, challenges to inclusion of women in research still exist. The OWRH has published strategies that may aid the recruitment and retention of women in clinical research.

Conclusion

Although regulatory policies governing research in women, minorities, elderly, and children have switched from a protectionistic to an inclusive stance, these populations are still under-represented in clinical research. The participation of individuals with cognitive impairment, inmates, and refugees in clinic research requires addressing special social and ethical challenges. The lack of participation in research by women and these other special populations result in a gap of medical knowledge regarding the health and appropriate medication use of these groups. In this paper, current policies from regulatory agencies, expert, and other advocacy groups are presented. Pharmacist-researchers should be cognizant of these guidelines and be an advocate for the inclusion and rights of women and other special populations in research.

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