

American Association of Clinical Endocrinologists

White Paper on Endocrine Clinical Research

Introduction - AACE Supports Endocrine Clinical Research

There are millions of Americans who are affected by endocrine disorders. For instance, according to the National Institutes of Health, as of 2003, nearly two-thirds of U.S. adults are overweight or obese (BMI \geq 25), numbering 129.6 million adults. Of these, 64.5 million are women and 65.1 million are men. In association with overweight and obesity, there are 18 million people age 20 years or older (8.7 percent of all people in this age group), who have diabetes mellitus. Obesity and diabetes disproportionately affect minority populations including Hispanics, Blacks, and Native Americans. Other endocrine disorders, including sex hormone deficiency, osteoporosis and thyroid diseases, also carry a significant burden on the population of the United States.

Clinical trials determine whether a drug or technology under development is safe and effective in humans. Prior to human clinical trials all drugs and technologies are tested extensively in animals. If the results of such studies in animals support the study of the drug or technology in man, based on rules and standards established by the Food and Drug Administration (FDA), then human clinical trials can commence. There are three sequential phases of clinical trials that are completed prior to FDA review and approval of a drug or technology:

- Phase I studies are small, brief, very closely monitored studies to establish basic safety and tolerability, generally performed in normal volunteers.
- Phase II studies are well controlled clinical trials, performed in a modest number of patients with the disease or condition in question, to evaluate efficacy, identify the best dose, and assess short term safety.
- Phase III studies are large clinical trials to evaluate the effect of the drug or technology in large numbers of patients with the disease to be treated over longer periods of time (if the drug is intended for long term use). The FDA uses the results of Phase III trials as the major basis for their review of the overall efficacy and safety of a drug or technology leading to approval for marketing.

Clinical research on drugs and technologies usually continues after initial FDA approval to explore potential additional characteristics or expanded uses of a drug or technology that go beyond the information required for the initial approval

AACE strongly supports clinical research on diseases that affect the endocrine system, and metabolism. Clinical research on these disorders helps to develop treatments that:

- prevent or delay morbidity
- delay mortality
- promote good nutrition and healthier lifestyles
- improve the quality of life for patients
- advance science
- help to address disparities in healthcare outcomes

Clinical Endocrinologist are Ideally Suited to Lead Research on Endocrine and Metabolic Diseases

The clinical endocrinologist has the in-depth, additional subspecialty training to understand and treat endocrine and metabolic disorders. Additionally, the clinical endocrinologist is at the forefront of care for patients with these disorders. The regular interaction with patients who are affected by these diseases provides the clinical endocrinologist the insight required to address areas of need.

AACE strongly supports the leadership of clinical endocrinologists in clinical trials of endocrine and metabolic disorders. As part of this support, AACE will:

- Convene and staff a Clinical Research Committee.
- Assist pharmaceutical and technology companies in reaching the expertise of the clinical endocrinologist community.
- Educate the practicing endocrinologist on clinical research.
- Bring a clinical research curriculum to endocrinology training programs.
- Promote the importance of clinical research with its members, and with the public.
- Advocate support for clinical research by funding authorities (NIH, VA, NGOs, etc.)
- Develop educational materials and handouts for patients.
- Develop and maintain web site materials on clinical research.
- Collaborate with other organizations (e.g., AAPP) on projects of mutual interest.

Clinical Research and Quality Endocrine Care

There are many types of published data. These include:

- Randomized, prospective, controlled trials (class A)
- Cohort studies (class B)
- Non-randomized trials with concurrent or historical controls (class C)
- Case-control studies (class C)
- Population-based descriptive studies (class C)
- Cross-sectional studies (class D)
- Case series (class D)
- Case reports (class D)
- Meta-analyses (class M)
- Review articles (class R)
- Consensus Statements or Reports (class R)
- Medical opinions (class X)

AACE strongly supports the development of practice guidelines which are based on quality outcomes data. AACE recognizes randomized, prospective, controlled, multi-center trials as the gold standard for the development of optimal practice guidelines. Only in the absence of this type of data should other types of reports be considered to formulate clinical practice guidelines.

Ethical Considerations Surrounding Clinical Research

Use of placebos in Clinical Trials for Endocrinology

Frequently, the best (and sometimes only) way to determine if a drug is effective and safe, is to compare it to placebo in an appropriately designed controlled clinical trial. It is widely accepted that comparisons

to placebo are ethical and good science when such studies are conducted with appropriate informed consent of the participants and review by a duly constituted Institutional Review Board (IRB). The justification for treating up to half of the patients in a clinical trial with placebo is that by virtue of their participation, these patients may benefit from new knowledge generated by the trial in the long run.

There is a need to develop more and better medications for endocrine disorders. Since placebo controlled trials often provide the best, most reliable information about the efficacy and safety of a drug, patients with endocrine disorders enrolled in clinical trials may face the prospect of treatment with placebo. AACE recognizes the need for placebo controlled trials. In this context, AACE emphasizes the importance of rigorous informed consent policies (see below), and the consideration of alternative protocol designs comparing new to established therapies, when appropriate.

Informed Consent

The law requires that a potential volunteer for a clinical study be given an informed consent form that explains the risks benefits and procedures that are involved in participating in the trial. Prior to protocols being approved, they are reviewed by an Institutional Review Board, to ensure they are ethical, and provide adequate safeguards for participants.

AACE supports an informed consent process that clearly outlines for the participant the following:

- The purpose of the research
- The expected duration of the research
- Any foreseeable risks or discomfort
- The benefits of participation in the research, either on a treatment arm, or on placebo
- Alternative treatments already in use that may be of benefit to the patient
- Measures to ensure patient confidentiality
- Means to obtain further information, or to resolve questions regarding the protocol
- The voluntary nature of participation in the study and the volunteer's right to withdraw from a study at any time and without prejudice.

Importance of Including Ethnic Minorities in Clinical Research Trials

According to the US Census, the American population was estimated at 280,540,330 in 2002. 77.7% of the population was classified as caucasian, Of the total population, 13.5% is Hispanic or Latino (all races), 12.8% is Black or African American alone, and 1.5% is American Indian or Alaska Native alone. Only 0.3% of the population is Native Hawaiian and Other Pacific Islander alone, but 4.5% of the population is of Asian race. As of 2002, 1.6% of the population is of mixed race. Altogether, about a fourth of the American population belongs to a growing minority or ethnic group.

The importance of the genetic background of an individual in determining the outcome from treatment has taken on additional importance in recent years. The field of pharmacogenetics has evolved from the observation that race and genetics do play a role in the outcome of a clinical intervention.

To date, few clinical trials have been conducted that specifically address the efficacy of a medication in minority groups. AACE strongly supports the design and implementation of clinical trials that address this need. AACE also supports the need for clinical trials in childhood disease prevention eg.(obesity , hypertension diabetes etc)

Conclusion:

AACE recognizes clinical research in endocrine and metabolic disorders as a critical component of optimal patient care. The clinical endocrinologist is ideally suited to lead clinical trials on endocrine and metabolic disorders. AACE strongly supports the involvement of clinical endocrinologists in the design, conduct, and interpretation of clinical research trials dealing with endocrine and metabolic disorders.