

"The Relevance of Ethnic Factors in the Clinical Evaluation of Medicines"

Stuart Walker, Cyndy Lumley, and Neil McAuslane, Editors, 1994, 280 pages, Kluwer Academic Publishers, \$233.00

Review by Norman M. Goldfarb

"The Relevance of Ethnic Factors in the Clinical Evaluation of Medicines" primarily consists of 17 essays based on presentations at a workshop held by the consulting firm CMR in London the previous year.

Clinical trials must reconcile two conflicting objectives: A subject population of homogeneous, healthy, genetically-similar subjects living the same lifestyle in the same environment yields the most definitive results... for that sub-population. On the other hand, a heterogeneous subject population with the opposite characteristics is most likely to identify sub-populations that experience unusually good or bad effects.

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Essential reading for clinical research professionals

Given the publication date of 1994, some of the information in the book may be dated. However, now that the transition to global clinical research is moving into high gear, the message is more timely than ever. It is hard to imagine designing or conducting a global clinical trial without first reading this book.

The scope of the book is broader than the title might lead one to believe. To start with, "ethnicity" goes beyond the genetics of race to include cultural factors such as lifestyle, diet, attitudes towards medical care, etc. The ethnicity of Blacks in Africa is thus very different than their ethnicity in the United States. The book also addresses cultural differences between countries such as attitudes towards disease diagnosis, medical care, and study conduct.

Pharmacokinetics – the effect of the body on drugs – and pharmacodynamics – the effect of drugs on the body – vary across ethnic groups (11%), but even more within ethnic groups (89%). For example, the incidence of rapid acetylation, a mechanism for metabolizing drugs, is 15% in Egypt, 40% in Canada, and 85% in Japan.

Some countries, such as Hungary, have relatively diverse genetics within the predominant race. Others, such as Japan, have relatively uniform genetics. In all races, however, there are sub-populations who look the same but respond differently to drugs, often in very substantial ways. Bimodal distributions are more common than smooth continuums because the genetic mechanisms are discrete mutations. Some people, for example, metabolize codeine into the active form – morphine – very slowly, and experience no analgesia at any plausible dose.

In addition to genetics, different ethnic groups have different diets, lifestyles, weights, muscle/fat ratios, age distributions, comorbidities (other diseases), concomitant medications, tolerance for pain, physiological theories, gender-based enrollment and retention rates, etc. In the United States, for example, many people take vitamins, herbal remedies and food supplements that have not been characterized for drug interactions, and may not be recorded on case report forms.

The book includes numerous fascinating examples of how genetic, environmental and cultural differences can confound clinical research. For example:

- Physicians in the United States generally treat to cure, physicians in Europe treat to manage disease, and physicians in Japan treat to maximize patient comfort.
- A hypertension study in South Africa showed large differences in drug effect between Caucasians and Blacks, apparently due to much-higher levels of salt in the Black subjects' diets.
- A study comparing the effectiveness of six antihypertensive drugs found that captopril was most effective in young and elderly Blacks and young Caucasians, but atenolol was most effective in elderly Caucasians.
- In a study of the antimicrobial loracarbef, Canadians reported adverse events – unrelated to the drug – four times more frequently than Italians.
- Neurovegetative hypotonia appears only in Germany, liver crisis in France, heavy leg syndrome in Switzerland, and tempero-mandibular joint dysfunction in the U.S.
- In England, feeling slightly unwell is described as “having a headache”, while in France, it is described as “feeling liverish”.
- Initiation visits in the U.S. are lightly-attended by investigators, while initiation visits in Japan are lightly-attended by study staff. As a result, training in both countries is compromised, but for opposite reasons.

The book is available at <http://www.cmr.org/> and bookstores.

Norman M. Goldfarb is Managing Partner of First Clinical Research, a provider of a clinical research best practices consulting, training, implementation and research services. Contact him at (650) 465-0119 or ngoldfarb@firstclinical.com.