

NIH Comments on the FDA Guidance Document 2003N-0529 Related to Racial and Ethnic Coding on MedWatch Forms to Collect Postmarketing Adverse Event Data

The NIH is pleased to provide the following comments in response to the FDA Notice: *Amending the MedWatch Forms to Collect Postmarketing Adverse Event Data Relating to Race and Ethnicity [Docket No. 2003N-0529]*. The NIH supports the collection of race and ethnic data as it relates to post-marketing Adverse Events. This approach will complement requirements for inclusion of minorities and adverse event reporting in the clinical research supported by the NIH in the pre-marketing environment. Nevertheless, the NIH would like to offer a number of comments and considerations along with background material that describes the data collection approach currently required for all NIH supported clinical trials. There would certainly be advantages to the development of a parallel system and we would be pleased to participate in discussions along those lines. Dr. Carlos Caban in the Office of Extramural Research at 301-435-2687 could help coordinate those discussions.

Please find below a summary of NIH comments including a list of advantages and disadvantages to the proposed data collection; comments related to the four questions that appeared in the Scope of Discussion section of the Notice; and finally a background section on related NIH requirements.

Summary of NIH comments

Data from post-market experience is collected to better understand the implications of adverse events on the overall safety of persons receiving any new treatment. Because of the understandable limits on the participation in most clinical trials and the potential for poor representation of individual subgroups, the proposed post-marketing data collection will be very important. Race and ethnicity has been shown to be an important although limited variable in understanding an event and identifying susceptible components of a treatment population. Race and ethnic classifications can clearly be correlated with the incidence and prevalence of a number of different diseases and heritable traits. There are also correlates with treatment-related behavior and access to health services, which may be important in a post-marketing environment.

It is frequently pointed out; however, that race and ethnic classifications are imprecise and can be poor surrogates of biological and genetic traits. Where practical, it might be more useful to record data by ancestral group as suggested in the FDA posting. Frequently, however, individuals, especially those in the United States, may not know their ancestry with a high degree of certainty. Lastly, clinicians and policy makers must use care in generalizing individual or small numbers of adverse events to all individuals with the same ancestry. Any information collected must be treated cautiously. In spite of the shortcomings, the advantages of collecting data on race and ethnicity clearly outweigh the disadvantages.

Advantages-

- ?? Having data on race and ethnicity may help to evaluate trends and differences in the safety and efficacy of certain drugs or treatment among sub-populations. Collecting such information may be helpful in identifying at-risk groups.

- ?? Having data on race and ethnicity may also help to explain the interaction of this information with other demographics (age, sex, and weight - questions 2-4) and relevant history/pre-existing medical conditions (question 7), and how these factors interplay in drug response and efficacy.
- ?? Data on race and ethnicity provide a measure of the social context that influences outcome and may be a surrogate for a complex demographic profile that integrates culture/SES/beliefs/health knowledge and that can be followed for trends.
- ?? The genetic basis of diseases has the underlying principle that there are subpopulations that bear more of the risk or susceptibility for certain diseases than the general population. It is clear from historical as well as more recent data that there are variations across racial/ethnic groups in terms of treatment responses and risk (particularly in terms of drug response/kinetics as a function of differences in drug metabolism among racial/ethnic groups, the classic being G6PD deficiency being more common in African Americans, and leading to difficulty metabolizing certain medications).
- ?? Another reason to record these categories is to monitor whether MedWatch reporting is being under- or over-utilized for any particular group

Disadvantages-

- ?? The data on race and ethnicity is imprecise and may be especially misleading if an individual identifies with 2 or more races.
- ?? Considering the lack of precision and relatively low rates of correlation with specific genetic and biological markers, there is the possibility of over-generalizing events and altering treatment policies beyond the specifically susceptible group.
- ?? Having race and ethnicity information may facilitate post hoc pharmacogenomic analyses, but the usefulness will be dependent on the availability of single nucleotide polymorphisms (SNPs) or other markers particular for each ethnic category that would allow differentiation. Most ethnic/racial populations are so diverse that any broadly-based analysis could weaken the benefit of collecting this information.
- ?? May raise ethical concerns about the labeling or profiling of individuals based on their race.
- ?? The patient may be suspicious of why race information is requested
- ?? Possible increased burden on the investigator or company.
- ?? With the proposed change, many would perceive race and ethnicity as tightly linked to biological processes, when, as OMB states, the categories are not to be interpreted as scientific or anthropological in nature.

Question 1: Should the MedWatch forms (Forms FDA 3500A and 3500) be amended with a special field or fields to capture adverse event data on race and ethnicity?

Yes, the MedWatch forms should be amended with special fields to capture race and ethnicity including detailed race and ethnicity information, in certain situations. (See the discussion on collection of information in international settings below)

The collection of the race and ethnicity data would be advantageous given the emphasis now placed on post-marketing data as agents receive accelerated approval. This is especially true for groups that are under-represented in the clinical trials that lead to approval. Important differences based, for example, on genetic polymorphisms may not become apparent until after approval, and post-marketing data collection would be as important as pre-marketing adverse event (AE) reporting in the identification of trends and leads.

Both race and ethnicity should be captured in domestic populations. Failure to collect and track this information limits the ability of individuals, in consultation with their health care provider, to determine whether a specific product is appropriate for them. It will help indicate the presence of a genetic, cultural, logistical, or environmental role for outcomes.

NIH requires the collection of race/ethnicity data from individuals in all clinical research projects that it supports. NIH also requires reporting of target data and annual cumulative enrollment data by sex/gender and race/ethnicity using the two question format. A parallel data collection in the post-marketing period could be very useful. (See the background section at the end of this document)

Specific Issues Related to International Reporting-

The FDA ICH E5 – Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data – defines ethnic factors that affect response in terms of both intrinsic and extrinsic issues, and provides a general framework for how to evaluate medicines with regard to their sensitivity to racial/ethnic factors. Differences in racial/ethnic factors have the potential to adversely affect some populations. These distinctions are important when the OMB racial/ethnicity categories are to be applied to foreign populations. The categories may be too broad to be useful in international studies, without additional information, and the collection of data according to these categories may not meet the ICH E-5 provision for identifying ethnic factors that may affect response to treatment. The data may not be sensitive enough for determining the scientific relevance of the ethnic differences in disease progress and response to treatment. Race/ethnicity reporting may only be appropriate for U.S.-based adverse events. Clearly it must be acknowledged that the only scientific way to distinguish differences is to relate all results to genomic distinctions.

If FDA decides to amend its MedWatch forms to capture racial and ethnic data in international settings, the choices for ethnicity and race as outlined in I.C.3. and I.C.4. are not sufficient. The addition of other subcategories that may be collapsed into the required ethnicity and race categories may well be needed. Since the pharmacological value of these categories stems from their loose overlap with ancestry, we recommend

that the link be more explicit in the choices for all situations. For example, as alluded to in I.C.5., “White” alone is not an appropriately informative category; “European Ancestry,” “Middle Eastern Ancestry,” and “North African Ancestry” should be used instead or in combination with the OMB Racial and Ethnic categories especially in international settings. While these terms may not cleanly branch from the five choices FDA outlined in I.C.4., these terms have more relevance to adverse drug reactions than the subjective and frequently misunderstood terms “Black” and “White.” Also, individuals should be able to choose more than one ancestry, similar to the ability to designate a multi-racial identity (I.C.2.). This may be more difficult logistically, and it will add statistical complexity. However, people have complex ancestries and this should be accounted for within any system attempting to collect this type of data. Ideally, data on the geographic origin of the individual’s ancestors at least two generations back should be collected. If these recommendations are too onerous, then the utility of collecting information through the OMB categories will be significantly diminished from a biological standpoint. Although potential correlations between adverse event data and racial and ethnic reporting may emerge, it will be impossible to draw meaningful biological conclusions from any observed trends.

Depending on how other countries report race and ethnicity overall, such data may not be generalizable. However, it may be useful in international reporting of post-marketing adverse events among broad ethnic or racial group categories. NIH has experienced real concerns when collecting race/ethnicity information in the international environment. In the U.S., race/ethnicity data is self-reported. The US OMB categories for race and ethnicity frequently lack meaning, cultural sensitivity and applicability when collected in other countries.

The following example may be instructive:

We recently went through lengthy explanations on the best way to collect race and ethnicity data with a PI who had a clinical site in Brazil. In order to comply with NIH policy, the 'foreign PI' is asked to design a culturally sensitive tool for collecting the data (via study volunteer self report) and then to take the reported ethnic, racial, and gender data and "fit it" the best way possible into the NIH Inclusion Enrollment Report Table for annual progress reports. As you can imagine, this presents all sorts of difficulties. We learned that in Brazil, for example, 66% of people think of themselves as mixed race; 40% claim to be white; and 4% claim themselves to be black. Apparently on birth certificates and military forms they recognize a category neither black nor white, called "Pardo"so 60% of people in the census reports conceive of themselves as Pardo.

Question 2: Should MedWatch race and ethnicity data distinguish between self-reported and observer-reported designations? If so, how should the designations be captured?

MedWatch data should distinguish between self-reported and observer-reported designations. The possibility for misreporting a person's race or ethnicity based on observation is great. Self-reporting should be the standard. If self-reporting is not possible, then the observer most likely to know the ancestry of the individual should report the race and ethnicity information (such as a first-degree relative per I.C.2.). However, whatever process by which this observer is identified should be specified in

the regulations and followed consistently. It is important that all researchers follow the same procedure for assigning race, ethnicity and ancestry in order to avoid compounding sources of error to what is, by its very nature, an imprecise measurement. Such distinctions should be made so that data can be compared based on self-reporting versus observational reporting. Observational reporting should be clearly marked, and if possible and not unduly burdensome, should be updated should self-reporting become possible. Possibly, a separate check-box should be placed next to the ethnicity and race section for self-reported race/ethnicity or observer-reported race/ethnicity.

Question 3: Would collection of race and ethnicity data on the MedWatch forms have an impact on the ICH E2B guidance relating to the electronic submission of adverse event reports ("E2B Data Elements for Transmission of Individual Case Safety Reports" (63 FR 2396 at 2397, January 15, 1998))?

Yes. Race and ethnicity data are not specifically addressed in the E2B Data Elements Guidance. The race/ethnicity data elements could be added in two ways. First, the data elements could be added under category "B.1. Patient Characteristics" as separate data fields. User guidance would need to describe how to handle United States data versus data from foreign sites in terms of the OMB race/ethnicity categories and the two question format. Separate electronic data fields in this section could enable analysis of the role of race/ethnicity as it relates to other information in the form. The number of additional data elements would be minimal, since the individual is reporting his/her own data.

Alternatively, the information request could be included under category "B.5. Narrative Case Summary and further information" in a manner similar to item B.7. of the current MedWatch form 3500. User guidance would be needed here also to describe how to handle US data versus data from foreign site. It is not clear what the compliance level is for filling out item B.7 for race/ethnicity data in MedWatch form 3500. However, it would require more staff work to receive the paper form and transfer it to an electronic database for analysis.

The ICH E2B Guidance was prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use (ICH). These changes would require working with the group to implement any suggested changes, and will take time. Since it will be guidance, and not mandatory, the database could be incomplete and bias any analysis.

Question 4: What is the financial impact associated with adding a special field or fields to the MedWatch forms to collect data on race and ethnicity?

Changing the forms to add a special field or fields to collect data on race and ethnicity would have a financial impact that varies on how it is implemented. Any change will require the development of educational venues and detailed instructions to facilitate broad understanding and compliance. If the forms are available electronically, the costs would include revising the electronic form as well as the underlying database to accept the data on the forms. If paper forms will also be used, then replacing the old forms with new forms may have a financial impact. There will also be costs associated with modifying relevant databases in addition to data coding costs associated with paper forms. In all cases, there are quality control issues that need to be built in to ensure the data is as accurate as possible.

Background Information on NIH Requirements Relating to Race and Ethnicity

NIH has implemented a number of policies and requirements for conducting research involving human subjects to ensure for their protection from research risks and to ensure appropriate inclusion of women and racial/ethnic minorities in research. Applicants are required to address these requirements for research involving human subjects in the Research Plan, section e "Human Subjects" of the PHS 398 Grant Application (5/01) http://grants.nih.gov/grants/funding/phs398/section_1.html#e_humansubs and the PHS 2590 Non-Competing Grant Progress Report(5/01) <http://grants.nih.gov/grants/funding/2590/2590.htm>. Policies on collecting race and ethnic data are available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>. Additional guidance and instruction for using the revised minimum standards for maintaining, collecting, and presenting data on race and ethnicity can be found in the PHS 398 (rev. 5/01) and PHS 2590 (rev.5/01) instructions and forms <http://grants.nih.gov/grants/forms.htm>. Comparable information will be provided in research and development contract solicitations and awards for intramural projects. This document should be used in conjunction with the instructions in the PHS 398 and PHS 2590 instructions and forms.

NIH is still making the transition from the combined race/ethnicity reporting format to the new OMB required format. Copies of the NIH formats are available as part of the guidance "What Form Should PIs Use for Population Tracking?" at http://grants1.nih.gov/grants/funding/women_min/pop_tracking_new_vs_old.pdf. Additional NIH policy documents and references on inclusion of women and minorities are available at http://grants1.nih.gov/grants/funding/women_min/women_min.htm.

NIH requires that investigators conducting clinical trials have a data and safety monitoring plan that has been approved by a registered IRB and by NIH program staff. At a minimum, all monitoring plans must include a description of the reporting mechanisms of adverse events to the IRB, the FDA and the NIH. For details especially as they relate to reports on race and ethnicity see the following policies:

- ?? NIH POLICY FOR DATA AND SAFETY MONITORING
<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.
- ?? GUIDANCE ON REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS FOR NIH-SUPPORTED MULTICENTER CLINICAL TRIALS
<http://grants2.nih.gov/grants/guide/notice-files/not99-107.html>.
- ?? FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.