APPENDIX

Studies of Efficacy in Subsets of the Whole Population; Enrichment

1.0 Introduction

Ideally, the effect of a drug should be known in general and in relevant demographic and other subsets of the population, such as those defined by disease severity or other disease characteristics. To the extent study patients are not a random sample of the patients who will be treated with the drug once it is marketed, the generalizability of the results can be questioned. Even if the overall result is obtained in a representative sample, however, that does not suggest the result is the same in all people. If subject selection criteria can identify people more likely to respond to therapy (e.g., high renin hypertensives to beta blockers), we consider therapy more rational and the drug more useful.

Subjects entering clinical studies are in fact almost never a random sample of the potential treatment population, and they are not treated exactly as a nonstudy patient would be treated. They must give informed consent, be able to follow instructions, and be able to get to the clinic. They are sometimes assessed for likelihood of complying with treatment. They are usually not very debilitated and generally are without complicated or life-threatening illness, unless those conditions are being studied. They are usually selected using particularly stringent diagnostic criteria that make it very certain they actually have the disease to be treated (more likely than in clinical practice). Lead-in periods are often used to exclude subjects who improve spontaneously or whose relevant functional measures (blood pressure, exercise tolerance) are too variable. Of course, the entire setting of trials is artificial in varying degrees, generally directed toward reducing unwanted variability and increasing study efficiency.

All of these departures from a truly unselected population of people likely to receive the drug are directed at identifying and including subjects likely to make a ''good assay population.'' They can be considered methods of ''enrichment'' of the population, modifications of a truly random sample of potential users to produce a population of subjects more likely to discriminate between an active and an inactive therapy. The kinds of enrichment described above are widely accepted and ''benign,'' i.e., it seems likely that results in such a population will be of general applicability, at least to patients with good compliance. There is a view, however, that in-use ''effectiveness'' may often be different from the artificial ''efficacy'' established in these enriched ''efficacy'' trials.

There are other kinds of enrichment that could also be useful but that would more clearly alter the inference that could be drawn from the results. This should not discourage their use but should encourage attention to what such studies do, and do not, show. Some enrichments of potential value include:

1.1 Studies of Patients Nonresponsive to, or Intolerant of, Other Therapy

In this kind of study, patients failing therapy on a drug, or failing to tolerate it acceptably, are randomized to the failed or poorly tolerated therapy or to the investigational treatment. Greater efficacy (or better tolerance) of the new therapy shows that the drug is useful in failures on the other therapy. This is a valuable showing if, e.g., the drug is relatively toxic and intended for a ''second-line'' use, but it does not show that the new therapy is superior in general, and such studies need to be carefully interpreted. By selecting study patients who will only infrequently respond to the control agent or who are very likely to have a particular adverse effect of the control drug, the design facilitates showing the second drug's advantage in that circumstance. A direct comparison of the two drugs in an unselected population that could contain responders to both drugs would need to be much larger to show a difference between the treatments, even if there was an overall advantage of the new drug. Moreover, it could be that each drug has a similar rate of nonresponders (but the other drug works in some of these), so that no difference could be seen in a direct comparison in unselected subjects.

In this design, it is usually critical to randomize the nonresponders or intolerants to both the new agent and the failed agent, rather than simply place the failures on the new drug. Patients who failed previously may ''respond'' to the failed drug when it is readministered in a clinical trial, or may tolerate the previously poorly tolerated drug in the new circumstance. This can present a problem. In the ''intolerance'' case, although subjects can be randomized to a drug that has caused certain kinds of intolerance, they cannot be randomized to a drug that would endanger them if administered (e.g., if the intolerance was anaphylaxis, liver necrosis). Similarly, in the nonresponder case, patients cannot be restudied on the failed drug if failure would lead to harm. In some cases, the prior experience may be an adequate control (e.g., failure of a tumor to respond), a baseline-controlled study design.

1.2 Studies in Likely or Known Responders

If patients cannot respond to the main pharmacologic effect of the drug, they cannot be expected to show a clinical response. Thus, subjects with no blood pressure response to sublingual nitroglycerin have been excluded from trials of organic nitrates, as they show no ability to respond to the mechanism of action of these drugs and including them would only dilute the drug effect. A similar approach was used in Cardiac Arrhythmia Suppression Trial (CAST). Only subjects responding to encainide or flecainide with a 70 percent reduction in ventricular premature beats (VPB's) were randomized to the mortality phase of the study because there was no reason to include people who could not possibly benefit (i.e., people with no VPB reduction). It is important in such cases to record the number of subjects screened in order to construct the study population so that users of the drug will have a reasonable expectation of what they will encounter. It will often be appropriate to incorporate similar selection criteria in labeling the drug for use.

The nitroglycerin and CAST enrichment approaches were generally accepted. A potentially more controversial enrichment procedure would be to identify responders in an initial open phase, withdraw treatment, then carry out a randomized study in the responders. This could be a useful approach when efficacy has proved difficult to demonstrate. For example, it has been difficult to obtain evidence that gut motility-modifying agents are effective in gastroesophageal reflux disease, perhaps because there are unrecognized pathophysiologic subsets of patients, some of which can respond and some of which cannot. It seems possible that identifying apparent responders clinically, then randomizing the apparent responders to drug and placebo treatments, would best utilize both clinical observation and rigorous design.

In seeking dose-response information, little is to be learned from studying the drug in a population of nonresponders (although one would want to know the proportion of the population that is nonreponsive). Such studies might better be carried out in known responders to the drug. Similarly, in evaluating a drug of a particular class, studies including only known responders to the class might be more likely to detect an effect of the drug or to show differences between members of the class.

Finally, it should be appreciated that randomized withdrawal studies (see section 2.1.5.2.4), and studies of maintenance treatment in general, are often studies in known responders and can therefore be expected to show greater effect than studies in an unselected population.

Dated: September 16, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy

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DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4442–N–12]

Notice of Proposed Information Collection for Public Comment; Housing Condition Assessment (Pilot Study)

AGENCY: Office of the Assistant Secretary for Policy Development and Research.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below will be submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act of 1995. The Department is soliciting public comments on the subject proposal.

DATES: *Comments Due Date:* November 23, 1999.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name or OMB Control Number and should be sent to: Reports Liaison Officer, Office of Policy Development and Research, Department of Housing and Urban Development, 451 7th Street, SW., Room 8226, Washington, DC 20410.

FOR FURTHER INFORMATION CONTACT: William E. Freeborne, Program Analyst, Office of Policy Development and Research, Department of Housing and Urban Development, 451 7th Street, SW, Room 8134, Washington, DC 20410–6000, telephone (202) 708–4370 ext. 5725. (This is not a toll-free number). A copy of the proposed forms and other available documents to be submitted to OMB may be obtained from Mr. Freeborne.

SUPPLEMENTARY INFORMATION: The Department will submit the proposed information collection to OMB for review, as required by the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35, as amended). This notice is soliciting comments from members of the public concerning proposed collection information to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) Evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information; (3) Enhance the quality, utility and clarity of the information to be collected; and (4) Minimize the burden of the collection of information on those who are to respond; including through the use of appropriate automated collection techniques or other forms of information technology, e.g. permitting electronic submission of responses.

Title of Proposal: Housing Condition Assessment (Pilot Study).

Description of the Need for Information and Proposed Use: Housing is the most basic and important part of the infrastructure in the United States and worldwide. Its direct and indirect impact on the economy and public welfare is far reaching. While increasing homeownership opportunities has benefits, it presents certain challenges to the future of housing in the United States. For example, housing production and resource utilization is stretched to meet the housing demand of a diverse and growing population. To continue to meet this demand, conventional methods need to be improved while innovative materials and methods need to rise to meet the challenge in a responsible, but competitive manner. This challenge can only be effectively met by better understanding the performance of the existing housing stock and developing improved technologies, including both design and construction practices that lead to better and more affordable homes for all Americans.

This study will help fill critical knowledge gaps to develop more durable products for single-family home construction. The work will help to establish a baseline of housing performance from which defects can be rationally identified and future improvements and innovations can be cost-effectively directed. The objectives are as follows:

(1) Pilot test and define the data collection methodology for potential use as a national housing condition assessment instrument.

(2) Establish a baseline of housing condition (durability), based on the pilot test data.

(3) Evaluate the housing condition assessment data to identify trends related to durability performance.

The housing performance assessment protocol will be implemented on a pilot scale. The focus will be on documenting conditions including products, homeowner maintenance, history of any damage, etc. The study will obtain a random selection (representative sample) of about 200 homes for site inspections and occupant/owner interviews in a pilot study region (Anne Arundel County, MD). Homes will be single-family detached, selected from property tax records according to the following age brackets: 5 to 10 years old and 25–30 years old. A data collection form will be created with detailed information to be collected from the sampled homes by field inspectors operating under contract to HUD.

Assessment teams will contact owners or occupants prior to site visits to conduct a phone interview and to arrange for an on-site assessment. The data will be recorded on field survey forms and then transcribed to a computer database. Homes not receiving voluntary homeowner participation will be subject only to a visual survey from the street.

Agency Form Numbers, if Applicable: None.

Members of Affected Public: A randomly selected group of 200 homeowners will be affected by the information collection.

Estimation of the Total Number of Hours Needed to Prepare the Information Collection Including Number of Respondents, Frequency of Response, and Hours of Response: Information will be collected by a telephone and a voluntary personal interview with a maximum of 200 randomly selected homeowners in the Mid-Atlantic Region. Each survey will take approximately 30 minutes or less to complete. This means a total of 200 hours of response time for the information collection.

Status of the Proposed Information Collection: Pending submission to the Office of Management and Budget (OMB) for review and clearance.

Authority: Section 3506 of the Paperwork Reduction Act of 1995, 44 U.S.C. Chapter 35, as amended.

Dated: September 10, 1999.

Lawrence L. Thompson,

Deputy Assistant Secretary for Policy Development.

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DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4432–N–38]

Federal Property Suitable as Facilities To Assist the Homeless

AGENCY: Office of the Assistant Secretary for Community Planning and Development, HUD.

ACTION: Notice.

SUMMARY: This Notice identifies unutilized, underutilized, excess, and surplus Federal property reviewed by HUD for suitability for possible use to assist the homeless.

EFFECTIVE DATE: September 24, 1999.

FOR FURTHER INFORMATION CONTACT: Cliffort Taffet, Department of Housing and Urban Development, Room 7262 451 Seventh Street SW, Washington, DC 20410; telephone (202) 708–1234; TTY number for the hearing- and speech-impaired (202) 708–2565 (these telephone numbers are not toll-free), or call the toll-free Title V information line at 1–800–927–7588.

SUPPLEMENTARY INFORMATION: In accordance with the December 12, 1988 court order in *National Coalition for the Homeless* v. *Veterans Administration,* No. 88–2503–OG (D.D.C.), HUD publishes a Notice, on a weekly basis, identifying unutilized, underutilized, excess and surplus Federal buildings, and real property that HUD has reviewed for suitability for use to assist the homeless. Today's Notice is for the purpose of announcing that no additional properties have been determined suitable or unsuitable this week.