

Special Interview

# Interview with Dr. Robert Temple on drug evaluation policy of FDA — Ethics, science of placebo-control and comparative effectiveness studies —\*<sup>1</sup>

**Robert Temple** \*<sup>2</sup>

Center for Drug Evaluation and Research  
Food and Drug Administration, U.S. Department of Health and Human Services

**Interviewer: Chieko Kurihara** \*<sup>3</sup>

Molecular Imaging Center, National Institute of Radiological Sciences (NIRS)  
(June 13, 2014, Washington D.C., United States)

## Abstract

This is the record of an interview with Dr. Robert Temple, Deputy Director for Clinical Science of the Center for Drug Evaluation and Research (CDER) and also Acting Deputy Director of the Office of Drug Evaluation I (ODE-I), Food and Drug Administration, U.S. Department of Health and Human Services.

Dr. Temple is one of the key-persons in the international debate on the ethics and science of placebo-controlled clinical trials, who greatly contributed to the ICH-E10 guidelines on the choice of control group, as well as 2008 revision of the Declaration of Helsinki, for its paragraph of the use of placebo control. In addition to this subject Dr. Temple has for a long time played a very important role in the establishment of FDA's philosophy and policies on clinical science, and has had an important role in many CDER and ICH guidances (ICH E-3, E-4, E-5, E-7, E-10, and E-14).

The wealth of ideas about clinical trial design discussed here could contribute to future perspectives that might contribute to more attention to individualized medicine, shifting the mega-pharma-approach of "one-size fit all."

## Key words

U.S. Food and Drug Administration, placebo controlled clinical trial, comparative-effectiveness study, enrichment study, clinical science

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\*<sup>2</sup> Office of Drug Evaluation I (ODE-I), Food and Drug Administration, U.S. Department of Health and Human Services

\*<sup>3</sup> Research Center for Radiation Protection, NIRS; Editorial staff, *Rinsho Hyoka (Clinical Evaluation)*



Interview was at the home of Dr. Robert Temple, Washington D.C., Maryland, United States, June 13, 2014.

Temple participates in the direction of ODE-I, which is responsible for the regulation of cardio-renal, neuropharmacologic, and psychopharmacologic drug products. Dr. Temple has a long-standing interest in the design and conduct of clinical trials and has written extensively on this subject, especially on choice of control group in clinical trials, evaluation of active control trials, trials to evaluate dose-response, and trials using “enrichment” designs.

Source: Web-site of the U.S. Food and Drug Administration (<http://www.fda.gov/Drugs/NewsEvents/ucm295045.htm>)

Dr. Robert Temple is Deputy Director for Clinical Science of the Center for Drug Evaluation and Research (CDER) and also Acting Deputy Director of the Office of Drug Evaluation I (ODE-I) in the U.S. Food and Drug Administration. He has served in this capacity formerly Director of ODE-I since the office’s establishment in 1995.

Dr. Temple received his medical degree from the New York University School of Medicine in 1967 and was a clinical associate at the National Institutes of Health from 1969 to 1972. In 1972 he joined CDER as a Medical Officer in the Division of Metabolic and Endocrine Drug Products. He later moved into the position of Director of the Division of Cardio-Renal Drug Products, which he held from 1976-1982.

In his current deputy position, Dr.

## 1. Establishment of FDA’s policy

**Interviewer** I greatly appreciate your willingness to accept this interview. There are two reasons I regard this as an extremely valuable opportunity: First, I have published some interviews with key-persons of the debate on ethics of placebo-controlled clinical trials<sup>1-5)</sup>, and you are the most important key-person. Another reason is that I know you have been playing a very important role in the establishment of FDA’s philosophy and policy of clinical science, the origin of which was the 1962 Kefauver-Harris Amendments which specified that drug approval should be based on two or more “well-controlled clinical trials”. From this second reason, the editorial board members of our journal, *Clinical Evaluation*, invited you to Japan in

1992 for a symposium with other of your colleagues of FDA<sup>6)</sup> (Photo, page 4). There have been a number of publications of Japanese translations of the FDA’s guidance since the 1970s.

**Temple** I remember when Prof. Naokata Shimizu first invited me to a meeting in Japan, about 30 years ago. Since then, I have had many opportunities to visit Japan.

**Interviewer** I believe that Prof. Shimizu, an editorial board member of this journal will be pleased about this interview. I found in the web-site of FDA<sup>7)</sup> that you have commented on the impact of the Kefauver-Harris amendments. The editor-in-chief, Dr. Masanao Kurihara says that you must be very much engaged in the process to realize this policy in FDA.

**Temple** Before the Kefauver-Harris amendments in 1962, there was no legal requirement that

a new drug be shown to be effective before it could be marketed. It only had to be shown to be “safe.” (You might ask how a drug that did no good at all could be safe if it had any adverse effects, but the law did not consider that). And people developing drugs rarely carried out the kinds of controlled studies that could reliably demonstrate effectiveness. Of course the effects of some drugs are fairly obvious (loop diuretics, many antibiotics) so that there were effective drugs even before 1962. But when we looked, as the 1962 law required, at the pre-1962 drugs, about 1/3 did not appear to work.

In 1962 the law was changed to require that for a drug to be marketed, there had to be “substantial evidence that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” Very importantly, the law went on to say that “substantial evidence” meant “evidence consisting of adequate and well-controlled investigations, including clinical investigations,” by qualified experts that support the conclusion that the drug actually had the claimed effect. Well, this changed everything, especially when, in 1970, we wrote regulations describing the properties of an adequate and well-controlled study.

The new law completely changed the data we received and since that time we, and much of the world, have increasingly applied the well-controlled study standard to any treatment, drug, biologic, medical device, and even many surgical procedures. I have long believed it has been a (maybe the) major contributor to medical progress in the last half-century (together, of course, with the development of the novel and valuable treatments that were put to the well-controlled study test).

## 2. Debate toward 2013 revision of the Declaration of Helsinki: Ethics and science of placebo control

**Interviewer** So I would like to start the issue of placebo. Since the 1996 revision of the Declaration of Helsinki (DoH), by the World Medical Association (WMA), there were 4 revisions related to use of placebo controls. In 2000 it was changed by WMA to say that placebo controls could be used where there was no effective therapy but that they could not be used for any condition if there was an available effective therapy. FDA and others objected to this, arguing that although patients could not be denied an available life-saving treatment, if no harm would come to patients from not using the available therapy, it was ethical to use a placebo-control in a fully informed, non-coerced patient. Moreover, as explained in ICH E-10<sup>8)</sup> there were many situations, especially for symptomatic treatments, where only a placebo-controlled trial could be informative. In those cases comparative or non-inferiority trials were uninterpretable when they did not show a difference between the treatments. FDA has recently elaborated on this in its draft Non-Inferiority Guidance. The WMA 2002 note of clarification attempted to correct this, allowing use of a placebo for a scientifically compelling reason OR if there was no additional risk of serious or irreversible harm, but that was a mistake. Even a valid methodological reason for wanting to use a placebo would not justify denial of a life-saving treatment. This was corrected in 2008, where it said that placebos were acceptable if there was a good reason for a placebo-controlled design AND patients would not be harmed. I know you believe that ICH-E10, finalized in 2000, had described the proper conditions for use of placebo controls long

before this.

**Temple** I believe that ICH-E10<sup>8)</sup> provides a very clear description of the ethics of placebo-controlled studies. As for the Declaration of Helsinki, almost everybody agrees with the 2008 revision. If you want to study a new drug in a life-threatening condition where there is some existing therapy, you have to compare the new treatment with the existing therapy; you can't deny it to patients. You can show superiority to the other treatment or non-inferiority. But for symptomatic conditions, you can ask people if they're willing to be in the study and be randomized to placebo, because whatever happens to them is temporary, i.e., discomfort, but not harm, and a patient can choose to accept that.

**Interviewer** I know your articles<sup>10, 11)</sup> on that point. I know that FDA changed its regulations on using foreign clinical studies not conducted under an IND (investigational new drug application) to support a marketing application in 2008 to remove references to the Declaration of Helsinki. Was that because of the placebo-control issue?

**Temple** It was not a direct response. What we realized was that a reference in any regulations to a document that we had no control over (such as the Declaration) was not prudent. So we referred instead in the regulations to the ICH – good clinical practice guidance, ICH E-6<sup>12)</sup>, which notes that many of its principles had their origin in the Declaration.

**Interviewer** It's nice to hear that you agree with 2008 revision, which is compatible with ICH-E10. I also believe ICH-E10 is almost perfect, but there is one thing I feel some concern. It describes a three-arm design as one that may resolve ethical problem<sup>13)</sup>, but even if you can decrease number of subjects assigned in placebo, it is not ethical if it may cause serious, irreversible harm, although three arm study may be better benefit/risk ratio for study population.

**Temple** You are quite right. The 3-arm design does not allow use of a placebo when denying available therapy would be unethical because that would cause harm. The design, including both a placebo and an active control (in addition to the test drug) helps interpret a study showing no difference between test drug and placebo by showing whether the trial had assay sensitivity, i.e., could distinguish an effective from an ineffective drug. In other words, it helps interpret a negative (no drug-placebo difference) study: did the test drug fail or did the study fail? If the active control did not beat placebo it indicates that the study could not tell us actual drug from placebo. It also can help interpret a comparative study; one would not expect to see a difference between 2 treatments if they could not be distinguished from placebo.

### 3. Standard care issue

**Interviewer** It's good to be able to hear your opinion like that. So how about the standard of care issue. If there is an existing therapy in the United States only, can you use a placebo control in developing countries?

**Temple** I think it depends on whether the treatment can be used in those countries and on the specific circumstances. There was tremendous controversy over an HIV study carried out in developing countries, mainly in Africa. The study was to see if an AZT regimen using only a single treatment would be effective in preventing fetal transmission. It was already known that the "076 regimen," which involved treatment before, during and after delivery, was effective. The new study compared a single dose AZT regimen to placebo, not to the 076 regimen. Many people wrote about it, e.g., Dr. Harold Varmus<sup>14)</sup>, Director of NIH, and people from Public Citizen's Health Research Group, Drs. Sidney Wolfe and Peter Lurie. There

were 2 reasons for the design (specifically use of a placebo control). First, the 076 regimen could not be used in the regions where the study comes to be carried out because there was no way to get all 3 AZT regimens to patients in the treatment environment. But second, and even more important, there was good reason to think that although the single dose regimen would not be as good as the 076 regimen, it might have an effect and it was critical to know whether this treatment worked at all. If they had compared it to the 076 treatment and it worked less well, they would not be able to tell whether it

had any effect at all. So, to see if it had an effect, they needed a comparison with placebo.

Although some, notably Wolfe and Lurie<sup>15)</sup>, said you have to compare the single dose to the standard regimen on ethical grounds, that would not have served the community's interest in finding a treatment they could actually use and that was at least somewhat effective. The reduced regimen, compared to placebo was found to be effective, probably not as good as the 076, but it was effective.

This issue came up at a WMA meeting in Brazil a couple of years ago; there was agreement that in

Photos at the time of symposium titled "Clinical and statistical aspects of drug approval" commemorating 20 years anniversary of Controller Committee. The lectures were published in *Clin Eval*. 1992; 20 Suppl 6.



From the right: Late Dr. Yorio Sato (Founding member of Controller Committee/Clinical Evaluation), Dr. Robert Temple (FDA), Dr. Robert T O'Neil (FDA), Dr. Stuart J. Pocock (London School of Hygiene and Tropical Medicine), Dr. Satya D. Dubey (FDA). This photo was previously published in *Clin Eval*. 1992; 20 Suppl 6.



Dr. Temple and Dr. Naokata Shimizu, editorial board member.



Second to the left: Dr. Temple; right: Dr. Masanao Kurihara, editor-in-chief



Dr. Temple, Dr. Kurihara and Tatsuo Kurokawa, editorial board member, who was at the Ministry of Health, now professor of Keio University.



a country that lacked an important treatment, and where there was no way the treatment could be used in that country, a placebo-controlled trial of a usable regimen was ethically acceptable.

For a poor country that doesn't have the best therapy and you really do want to know whether something less than optimal works or not, that seems perfectly reasonable.

#### 4. Post-trial access

**Interviewer** So how about the issue of post-trial access?

**Temple** We do not require that it be provided, but a lot of companies make it available. I don't think that should be a requirement, and the current Declaration doesn't say it is a requirement<sup>16)</sup>. What it now says is you should tell people what's going to happen. In the 2008 revision it said at the end of the study everybody should get the drug if it's effective. But you don't know whether it's effective at the end of the study; you haven't done the analysis yet; and you probably need two studies to know

whether it's really effective.

**Interviewer** There are some bioethicists saying that "instead of" or "in addition to" post-trial access, there should be "fair benefit". For example, Dr. Ezekiel Emanuel and his African colleagues wrote a paper<sup>17)</sup> to propose a concept of "fair benefit".

**Temple** This is a difficult question; if there's too much benefit, maybe it's an inappropriate inducement to join the trial. And suppose the condition is chronic. If you do an anti-depressant trial in a poor country, do you have to treat their depression for their whole lives? I don't have answers here but it is difficult.

#### 5. Comparative effectiveness study

**Interviewer** Thank you for your comments on the Declaration of Helsinki. I have read many of your papers, power point slides, and interview talks, so it's really great to be able to see you and discuss this topic. So I would like to move to some other aspects of clinical trial design. First, I would like

to discuss comparative effectiveness studies.

**Temple** Okay in most areas we do not see very many good studies.

**Interviewer** It is not mandatory for the approval of the drug.

**Temple** Definitely not, unless there is an existing treatment that affects serious (generally irreversible) morbidity or mortality. In that case the only ethical studies will usually be comparative studies, either to show non-inferiority or superiority, or studies that add the new therapy to the standard of care (add-on study). Certainly we see many such trials in oncology and in serious cardiovascular disease (atrial fibrillation treatment with anti-coagulants, treatment of acute coronary syndrome).

**Interviewer** But after approval, for a Phase 4 trial, if the pharmaceutical company intended to conduct a study to show superiority and include this claim into the label, or promotion, it should be conducted under the FDA's regulations<sup>18)</sup>. Right?

**Temple** Studies to support labeling claims or promotion do need to be conducted under an IND. And such claims would generally have to be supported by controlled studies, probably two of them. It's not common to seek such claims but it does occur. We have two angiotensin receptor blockers (ARBs), for example, that did studies comparing themselves with other ARBs, and they did have a larger blood pressure effect and the drug label says that. Of course many oncology drugs will be tested against the standard of care, usually seeking to show superiority, or as add-on to the standard treatment. Some anti-coagulants and anti-platelet drugs have shown advantages over the standard drugs they were compared to.

**Interviewer** You say it's not common, do you mean that it is uncommon within the range of FDA's regulations? I think that there are many clinical trials of head-to-head comparison using 2 or more approved drugs. Most of them are conducted by

federal funding, under 45CFR46 "human subject protection" regulations, do you mean?

**Temple** Well, where patients have to receive treatment, e.g., with anti-coagulant in atrial fibrillation or anti-platelet drugs in acute coronary artery disease, you of course do see comparative studies. But where they are optional, I don't think there are that many, even funded by the government, although ALLHAT<sup>19)</sup> and CATIE<sup>20)</sup> are clearly examples of such studies. If the federal government, rather than a commercial enterprise funds the trial, using marketed drugs, no IND is needed. But if a drug company supports the trial, the intent is fairly clear to include it in labeling and an IND is needed under the IND regulations.

**Interviewer** Could there be a clinical trial where the pharmaceutical company is the sponsor but there is no intention of new label or no intention of promotion? Can you imagine such kind of trial?

**Temple** Well, I guess anything is possible, but I would argue that such a trial always needs to be done under an IND. And that's a good idea for other reasons. We can help a manufacturer understand what design the trial needs to get a claim. For example, suppose you compare your drug to a dose of another drug that too low; i.e. it's not the full dose. We had a manufacturer of an angiotensin receptor blocker (ARB) that wanted such a claim, but the first study they did they used too low a dose of the comparator drug. So we told them this would not support the superiority claim. They then had to do two more studies using a full dose. In case of cancer drugs, studies often show that new drugs beat the standard of care, so you see that all the time. But, as I said, once you leave that area, it's fairly unusual to see comparative studies. There's no antidepressant that has a claim that it's better than another one, for example.

**Interviewer** One of the reasons why people



want to see comparative studies that the FDA approved many drugs that are not very effective because many of these were compared with placebo.

**Temple** Well, that goes to another whole question, one that is addressed in our draft non-inferiority guidance<sup>9)</sup> and ICH E-10<sup>8)</sup>. How can you show that a drug is effective without a placebo-controlled trial? You have to do a formal, rigorous, non-inferiority study, and these are done where outcomes are well-defined for the control drug; e.g., we know the effect of Coumadin<sup>®</sup> in preventing stroke in atrial fibrillation or of clopidogrel in preventing heart attacks in people with acute coronary syndrome; we know the effects of antibiotics in a range of diseases; we know the effects of anticancer treatments. In those cases a non-inferiority study can be done because we know the effects of the control drug. But for symptomatic treatments, it is very hard to know the control effect, so that doing a non-inferiority study in a symptomatic condition is almost impossible, and you will need a placebo control. As I noted, we have a whole draft guidance

on how to do a non-inferiority study. It is, of course, perfectly all right to do a comparison of 2 drugs in addition to a placebo comparison.

## 6. Enrichment study

**Interviewer** So, how about enrichment study? Do you think it should be promising approach?

**Temple** Well, we have a draft enrichment guidance also<sup>21)</sup>. It describes a variety of enrichment maneuvers, and some could relate to comparative claims. One interesting one is to take non-responders to previous therapy and randomize to a new drug and to the failed drug. It would be of great interest to practitioners to know how to treat patients who fail standard therapy. But only 4 trials like this have ever been done, as far as I could tell, and 3 were successful. They allowed drugs that would not have been approved otherwise (because of toxicity) to be approved. We would never have approved clozapine (with its 1.5% rate of agranulocytosis) unless it was better than the alternative drugs in people who failed the other



treatment. In the critical study, they took people who had failed to respond to haloperidol, then randomized to a drug like haloperidol or to clozapine and clozapine was far better.

**Interviewer** How about the CATIE<sup>20)</sup> study?

**Temple** CATIE was a large comparative study that NIMH (National Institute of Mental Health) researchers conducted. They studied 5 antipsychotic drugs, looking at dropouts and the cause of dropouts (was it because of intolerance or because the drug did not work?). Olanzapine was better than the others with respect to dropouts for lack of effectiveness but it had more dropouts for toxicity, e.g., weight gain.

The enrichment design using the non-responders, and randomizing to the failed and new drug, is really of interest. Even if your drug isn't better overall, if there are some people who respond better to it than to the other drug, you can detect this in such trials and it would be important to know. Of course, drugs don't always work in people who fail other therapy. We've had a lot of public discussions about non-steroidal anti-inflammatory drugs, and their toxicity. Vioxx<sup>®</sup> (rofecoxib), you recall, was removed from the market because it caused an increased rate of heart attacks. Merck then did a study in which they took people who had failed to respond to Celebrex<sup>®</sup> (celecoxib) and randomized them to Celebrex or to Vioxx. I would have bet that Vioxx would be better for those people, because rheumatologists believe that people are individualized in their responses to these drugs. But the study showed no difference between the two drugs at all.

**Interviewer** I agree with you concerning the issue happening in U.S.. So in Japan, there was one interesting misuse case<sup>22, 23)</sup> of ICH-E10, which may be one of the misuses of an enrichment study. Sertraline was approved in Japan in 2006, 15 years later than in the Western countries. The company

conducted 2 pivotal studies in Japan of active-control (because placebo control used to be very difficult at that time) and failed to show non-inferiority. Therefore, they conducted a placebo-control randomized withdrawal study. A regulator gave them this idea saying that this design may mitigate the ethical dilemma, as it is explained in ICH-E10, which was just being finalized at that time. They conducted a withdrawal trial for the acute phase patients of major depression<sup>24)</sup>. It means that they proved only relapse prevention for non-responders in the acute phase. However, it was allowed to claim more general effects for depression, seeing substantial foreign data. In the brochure of post-marketing survey, it was written that the drug could not show non-inferiority to other active drugs. Therefore an association of clinic psychiatrists worried it may cause law suits claiming that they prescribed a less effective drug. Once they boycotted this drug, but then after some struggle, this drug came to be used commonly. This is a somewhat funny story.

**Temple** I'm not sure I follow all of this, but a few points. We would never consider a comparative trial of an antidepressant that showed no difference from a control to be evidence of effectiveness. You need a placebo group. We have to date expected evidence of effectiveness in acute depression to support a claim for treatment of acute depression (and sertraline has such studies). We very much want to see maintenance studies as well, showing that continued use decreases the rate of recurrent depression. To date no one has received approval solely for maintenance (i.e., prevention of recurrent depression), but it is a possibility.

**Interviewer** I wanted to ask you about approval of valsartan (one of ARBs) for heart failure. More than 80 countries, including of course U.S., approved new indications of heart failure or therapy after heart attack, based on GCP trials<sup>25, 26)</sup>,

including double-blind placebo control trials.

**Temple** Well, valsartan has the heart failure claim.

**Interviewer** Except Japan.

**Temple** The study was somewhat unusual. The trial was designed to add valsartan to an ACE inhibitor and show added benefit. But not everybody in the trial could tolerate an ACE inhibitor. So they tried to put you on an ACE inhibitor but 7 percent of the population couldn't take an ACE inhibitor. In that 7 percent, the trial was therefore valsartan versus placebo. In the group that got the ACE inhibitor, valsartan seemed to add somewhat to the effect but when you looked closely, it added most clearly when the dose of the ACE inhibitor

was less than the full dose. But in the 7 percent of people who couldn't tolerate an ACE inhibitor- i.e., valsartan versus placebo- (which was only 300 people), there was a 50 percent reduction in mortality. So we gave them a claim for people who can't tolerate ACE inhibitor.

**Interviewer** It's very interesting, but in Japan this type of study may be difficult to conduct.

**Temple** Why?

**Interviewer** There are some reasons. First, in Japan it is difficult to conduct placebo-controlled trials of authorized drugs.

**Temple** Well, being on an ACE inhibitor saves your life, so we too would not allow a trial of valsartan versus placebo in everyone. But in these



people who couldn't tolerate an ACE inhibitor and who were on a diuretic, and a beta-blocker, we would allow it.

**Interviewer** Not only the placebo issue, it is also difficult for Japanese researchers to conduct sound scientific phase 4 studies. The second reason is that in Japan there are two different sets of regulations for clinical trials: GCP under the Pharmaceutical Affairs Law and governmental guidelines for clinical research. There is a tremendous discrepancy between these two sets of regulations. This tremendous discrepancy affects the cost of trials. So the number of academic researcher's GCP trials is very small, although it is increasing thanks to the efforts of many people's. This is completely different from U.S. situation where many of academic researchers conduct IND trials using public or private funding. For Japanese companies also, it is much too expensive to conduct phase 4 trials under GCP. Therefore, companies provide unrestricted funding to academic researchers and these researchers conduct clinical trials. Some of these reports may be based on manipulated data, or at least, biased data. Many of the company persons assist Japanese researchers in writing their manuscripts to be submitted to top journals. These inappropriate relationships have been well known for a long time but only recently came to be "socially" criticized after the Novartis scandal <sup>27)</sup>. In Japan the culture of conducting sound science, especially ethical phase 4 studies is very much immature.

**Temple** That's interesting. Such kind of trials are being done all over the world now. I mean that's really quite striking.

## 7. ANPRM and future perspective

**Interviewer** Now I would like to ask you for your perspective on the proposal of new rule from the Department of Health concerning what you call

ANPRM <sup>28)</sup>.

**Temple** Yes, it is the huge rule. It touches on dozens of topics.

**Interviewer** There are several topics specially Japanese people are interested in: risk-based approach; broad consent; central IRB; and expanding the scope of the regulations.

**Temple** We encourage use of central IRBs to promote efficiency <sup>29)</sup>, but people really want their local control, so they are not widely used.

Also we issued a guidance on risk-based monitoring <sup>30)</sup>. That's already permitted under ICH-E6. It says the amount of on-site monitoring needed depends on the study and you might not need any. But companies fear that we would find errors if they fail to monitor extensively.

**Interviewer** Thank you that you provide such comments. So could you provide your future perspectives, near future? What is your most important job at FDA?

**Temple** Well, I have two jobs. I'm called deputy center director for clinical science. So that's one thing. I am very involved in quite a lot of guidance, e.g., the guidances on enrichment designs and non-inferiority studies, multiplicity, and adaptive design. You know we're very interested in using more efficient designs and thinking about what the endpoint should be. I'm also still deputy director of what's called ODE-I. ODE-I has cardiovascular, neurologic and psychiatric drugs. So it keeps me in touch with the real world.

**Interviewer** I greatly appreciate you for giving your precious time for this interview.

**Temple** Okay. I enjoyed the conversation.

### Acknowledgement

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