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A pioneer in menopause research, Dr. Utian founded the world's first menopause clinic in Cape Town, South Africa, in 1966 and established the Cleveland Menopause Clinic in 1983.

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Precisely Defining the Effects of Long-Term HRT— The Ultimate Catch-22

Remember Joseph Heller's 1961 novel *Catch-22*? "There was only one catch and that was Catch-22, which specified that a concern for one's safety in the face of dangers that were real and immediate was the process of a rational mind. Orr was crazy and could be grounded. All he had to do was ask; and as soon as he did, he would no longer be crazy and would have to fly more missions. Orr would be crazy to fly more missions and sane if he didn't, but if he was sane he had to fly them. If he flew them he was crazy and didn't have to; but if he didn't want to he was sane and had to. Yossarian was moved very deeply by the absolute simplicity of this clause of *Catch-22* and let out a respectful whistle. 'That's some catch, that *Catch-22*,' he observed. 'It's the best there is,' Doc Daneeka agreed.'" (www.webster.edu/~barrettb/heller.htm)

Attempts to precisely define the true benefits and risks of long-term hormone replacement therapy (LTHRT) after menopause pose an exquisite dilemma, perhaps the ultimate *Catch-22*. We need randomized, controlled clinical studies to evaluate the precise outcomes of LTHRT on real end-points, such as fractures of the hip and spine; coronary heart disease events; incidence and outcome of breast, ovarian and other cancers; incidence and progress of Alzheimer's disease and so forth.

Obtaining this information necessitates enrolling large numbers of women in studies that, of necessity, take many years to plan, complete and report. But by the time such randomized, controlled, blinded long-term studies are completed, the drugs, doses, regimens or combinations will almost certainly have changed. Thus, by the time this planned, long-term study is reported, the healthcare provider will have moved on to prescribing different products, regimens or doses. We need the studies in order to know the outcomes and, therefore, to justify what we are doing, but by the time we do the studies, the answers don't reflect what we are currently doing. *Catch-22!*

The Women's Health Initiative (WHI) is a perfect example of this problem. WHI was planned in the 1990s, is being executed over the course of a decade as one of the most expensive clinical research projects ever supported by the NIH, and findings will be reported in detail later this decade. By that time, at the very least, the preferred doses and, almost certainly, the preferred progestogen, will have changed.

What is the answer? Epidemiologists maintain that we can rely on their mechanisms of evaluation of risk and outcome. Clinicians, third-party payers and the public demand "evidence-based medicine" parameters to justify the therapy. Each party criticizes the others as being unable to definitively answer what is the key question at this time: What are the precise outcome effects of currently used regimens of LTHRT?

Does anyone out there have any great ideas for resolving this *Catch-22*?

A handwritten signature in black ink that reads "Wulf H. Utian". The signature is written in a cursive, slightly slanted style.

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