

Jerald Silverman, DVM, Column Coordinator

Death as a study endpoint

Dr. Angel Gomez, a noted virologist, was developing a vaccine against the new H2N3 subtype of swine influenza virus. Because the virus can also infect ferrets, Gomez intended to use both pigs and ferrets in his research. He planned to have one group of each species immunized against the virus with another group serving as nonimmunized controls. Both immunized and nonimmunized animals would be challenged with the virus, with the expectation that only the nonimmunized ones would develop clinical signs of the disease.

On his IACUC protocol form, Gomez indicated that he would use a sufficiently high titer of virus to induce clinical disease, but based on field cases of flu in pigs, he believed that *severe* clinical disease would be exhibited in only the nonimmunized

ferrets. He proposed letting the disease run its course, which could lead to death of some ferrets. The IACUC questioned the logic of this strategy, asking why the death of the ferrets was a needed endpoint, since most pigs recover from influenza virus infections in a few days. Gomez agreed that the disease was likely to be much less severe in pigs, but he needed to use the very sensitive ferrets to test the true efficacy of the vaccine. He said that death, if it were to occur, was a needed endpoint, particularly for the nonimmunized animals, because it was necessary to know whether any of those animals might spontaneously recover from the induced disease.

After deliberating on the protocol, the IACUC said that it would approve the study if Gomez modified it to allow the veterinary

staff to treat any ferret health problems that were secondary to the flu virus, such as nasal congestion or bacterial infection. The intent was to make the animals somewhat more comfortable without interfering with the study's goals. However, Gomez balked at the request, saying that any form of treatment might interfere with the animals' immune response, which needed to be evaluated as part of his research. When questioned about what interference or other effects these proposed treatments might cause, he responded that he could not predict such effects and therefore it was necessary to leave the ferrets untreated.

Do you agree with Gomez or with the IACUC about the treatment of clinically ill ferrets? Is death a necessary endpoint for Gomez's research?

RESPONSE

Try a pilot study

Kimberley Cohen, MS, DVM &
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The veterinary staff should provide supportive care as recommended by the IACUC, with the participation of the investigator. The IACUC agreed that death would be an acceptable endpoint after review of the scientific justification so long as "procedures involving animals will avoid or minimize discomfort, distress and pain"¹. This request is reasonable and can be accomplished in tandem with the investigator, so that he can obtain valuable data while still meeting the requirements of regulatory bodies.

We note that the investigator has not presented any preliminary data on the reaction of the ferrets to the virus and

cannot adequately predict the extent of the disease in these animals. His reference is extrapolated from the observed reactions in swine. A small pilot study might be an appropriate alternative to determine the development and course of the induced disease in the ferret. This would allow for close monitoring and documentation of various time points that could be used to determine when death is likely to occur, if at all. Data from a pilot study could then be utilized to determine appropriate endpoints that would minimize animal suffering and distress, as well as avoid death as an endpoint. In addition, a thorough literature search may determine whether any information on the course of disease in the ferret is available to help delineate time points. This seems especially relevant given the common use of this animal model for influenza.

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1. The Animal Welfare Act (AWA) regulations (Code of Federal Regulations, Title 9 Subchapter A).

RESPONSE

Consider non-medical treatments

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How can the doctor claim that the virus titer is sufficient and that any treatments of secondary symptoms will affect the study, if he can make no prediction as to what changes may be induced? Both immunized and nonimmunized animals deserve treatment for secondary complications to the virus. Humans will take cold medicine to relieve symptoms of influenza, although it does not remedy the rhinovirus; over-the-counter flu medication only relieves symptoms and not the actual virus. Influenza symptoms are similar for different species, even with