Forum on the Use of Animals in Research

Friday, 11 May 2018 (11.45 – 13.15)

In memoriam, Dr Harry Blom
ECVO thanks Dr Blom for his valuable contribution, and for so generously giving his time to attend this Forum at a time when he knew he was terminally ill, and had a short time live. Thank you.

Transcript

Peter Bedford opened the meeting and welcomed everybody attending the Forum. He briefly explained that a European Directive was established in 2010 to harmonize the role of animal use in experimentation across Europe. Its aim was to address the 3Rs Principles. The 3Rs stand for the replacement of animals wherever possible, the reduction of number of animals being utilised and refinement of research protocols. This concept was first put forward by Russell and Burch in 1959 and its incorporation into almost all international laws on animal research accelerated its adoption. He explained that during the 2016 ECVO AGM, Jane Sansom raised the issue of the use of live animals in research. She was actually asking if the ECVO could accept only non-invasive research for the selection of research abstracts for the ECVO awards, research abstracts and publications and the result is today's Forum.

He handed over to Charlotte Keller, chairing the Forum. She thanked everybody for coming and asked the audience to prepare questions for the end of the forum where a discussion would take place with the four speakers.

Charlotte Keller introduced the first speaker, **Dr Harry Blom** (sadly deceased 2019).

Dr Blom is from the Animals Welfare Body Utrecht, Utrecht University, The Netherlands. Dr Harry Blom graduated in Biology, obtained PHD in the 'Effective housing conditions on laboratory animal welfare' at the University of Utrecht. He worked as staff member at the Animal Welfare Centre at the Utrecht University and at the same time served as a project manager for the European Commission. One of the projects focused on the implementation and enforcement of a specific EU Directive on animal experimentation. Another project focused on the harmonization and enhancement of training and education in live animal science in the EU. He is currently working as a laboratory animal welfare officer at UU and University Medical Centre in Utrecht. He has a huge and vast experience in laboratory animal welfare.

What makes an experiment with animals an animal experiment: a short introduction to the EU Regulations for the use of animals for scientific purposes
(Harry Blom)

Harry Blom thanked ECVO for the invitation and briefly introduced himself and explained that he worked as Project Manager at Utrecht and had a vast experience in laboratory animal welfare.

He explained that he was going to give a short introduction to the EU legislation for the use of animals for scientific purposes.

He explained that the Directive 2010/63/EU was issued in 2010 by the European Commission and enforced by the European Parliament and the Council of Ministers. He added that this was a new Directive to replace the first one from 1986. He noted that the European Commission issues directives in any type of field which then needs to be implemented in all 28 EU member states and that this had been done for the EU Directive 2010 as well.

He explained that the Directives stated in the first article that the 3Rs Principles of Russel and Burch (replacement, reduction and refinement) shall be applied wherever possible. He extended that the 3Rs Principles clearly state in the first article, that the use of live animals is forbidden for scientific purposes if any other method could deliver the same data. However, it also states that if there is no alternative available, then the scientist should use proper statistics, the right experimental design and to come up with the least number of animals needed.

He explained that in the Directive, the animal welfare plays a major role stating that the scientists need to make sure that the used animal is in the best possible physical and mental condition. The discomfort should be reduced to the absolute minimum level. It is important that the animals are in good physical and mental condition to generate adequate data for good science.
He said that the Directive is a big document and he could speak about it for hours, but he prefers to bring up some particularly important aspects.

He first wanted to draw the attention at the institutional level.
If a company, an institute, a university or a private practice wanted to involve animals in research, it first needed to ask permission from the competent authority for a user or breeder or supplier license. For instant universities or companies can have more than one.
The institution needed to have the appropriate housing and care facilities as outlined in the Appendix III of the Directive. He pointed out that there was a lot of information available on what was required, e.g. size, floor should be solid, group housed, social groups as in nature, extras such as a good place to sleep, toys items (for environmental enrichment) needs to be put in place. He added that there was no such regulation for pet animals.

The institute or company should also install an Animal Welfare Body (AWB) of scientists and other persons responsible for the internal oversight over the wellbeing of the animals before, during and after the research is carried out. There needs to be a veterinarian serving as an advisor to the AWB and these two parties should work closely together. Every institution should provide all the information and data on animals in house being used in animal research.

He added that the institute or company must ensure that the scientist and all involved staff needs to be adequately educated and competent and continuously trained. Skills in education should be kept to the appropriate level by continuous personal development (described in Appendix 5).

For each individual animal experiment regardless of whether invasive or non-invasive the time period of five years should not be exceeded. A detailed study protocol must be maintained outlining the procedures, with all discomfort the animal would experience listed.
This proposal must describe, the ethical assessment, the relevance and importance of the study.

This proposal then needs to be scientifically assessed by one or two committees and then also ethically (cost benefit assessment) assessed with regards to benefit, harm e.g. pain, stress and discomfort of the animals.

He then stated that the Directive also notes on origins of animals used in Appendix number I. He explained that, e.g., dogs and cats must be obtained from a licensed breeder which breeds animals just for the purpose of research. You can ask to use pet animals, but this is only allowed if the competent authority has given permission and you have a license to do so.

Appropriate methods for marking are necessary.

He then noted that there are of course exceptions that are not governed by the Directive.

He then referred to the definition of Animal Experiment and explained that it was defined by the Directive as an invasive or non-invasive experiment that involved:

1. The use of live animals
2. Non-human vertebrate or cephalopod species
3. Experimental, other scientific or educational purposes
4. He explained that in the proposal also the purpose should be described (long lists of purposes listed in the Directive, e.g. fundamental purpose, applied scientific purpose, educational purpose, toxicity testing).
5. One or more procedures that cause a level of discomfort equivalent or higher than that caused by the insertion of a needle in accordance with good veterinary practice.

He added that this definition also applied to the use of larval forms and foetal forms of mammals in the last third of their normal development.

With regards to point 4, he explained that the pain level is defined here. In order to consider it as animal experiment, the animal needs to encounter a certain level of pain or discomfort. He also mentioned that even non-invasive tests can cause stress levels leading to discomfort greater than that resulting from the insertion of a needle.

He added that 4 different levels of discomfort are defined:

1. Terminal (procedures under terminal anaesthesia with animal not waking up afterwards)
2. Minor
3. Moderate
4. Severe

A list of examples is to be found in Appendix 8 of the Directive.

He then explains that there are exemptions (which are not covered by the Directive) and he wants to discuss the following 3 as being very relevant to the audience:

1. Non-experimental clinical veterinary practices - procedures and techniques performed by veterinary surgeons for diagnostic purposes, e.g. taking blood or biopsies from a few individuals for diagnostic purposes, imaging. All for the animal benefit and not for scientific purposes.

2. Veterinary clinical trials required for the marketing authorization of the veterinary medical products, e.g. drug efficacy testing: for a new drug or an existing drug for a new species. These are also exemptions.
3. Procedures not inflicting any discomfort equivalent or higher than that caused by the insertion of a needle in accordance with good veterinary practice.

He thanked the audience for the attention and closed his speech.

Charlotte Keller introduced the second speaker, **Dr David Morton**.

Dr Morton is from England and has expertise and experience is in biomedical ethics and animal welfare. He graduated in veterinary medicine in Bristol, completed a PhD, performed research and moved to Leicester Medical School specialising in laboratory animal medicine and human anatomy. He then moved to Birmingham University where he set up the department of biomedical ethics. He is an ethic advisor to the European Commission on research applications involving animals and humans and he is the past-president of the European College of Animal Welfare and Behavioural Medicine.

Veterinarian Involvement in Animal research: Dilemmas and conundrums (David Morton)

David Morton started his speech in noting that himself and Harry have been involved with the Directive for many years. He noted that he had taken a slightly different view as he was involved in the so called "recognised veterinary practice". Human-animal interaction is what he is interested in. He looks at the ethics of people interacting with animals, not only in zoos and farms but also in research. In the animal research and in animal welfare legislation, there is an exemption for people carrying out research. He explained that if a person carries out research, and that research involves techniques that would normally be considered as being cruel to an animal, they are licensed under the animal research legislation to avoid prosecution under animal welfare legislation.
There is an exception for veterinarians carrying out clinical research as it is judged to be of benefit to the animals involved. But if it is known not to be of any benefit then they may be prosecuted under the animal welfare legislation. For example if you are a vet and are performing a cruel act for a cosmetic reason e.g. docking a puppy's tail, you may be prosecuted under the animal welfare legislation, but if you are a vet and doing it for a therapeutic purpose then this is OK.

He said that undoubtedly there have been tremendous benefits in the past from the classical clinical research, particularly if you think about infectious diseases e.g. vaccinations against cat and dog diseases etc. Vaccinations are tremendously important as they have protected the lives of millions of animals over the years.

The other things he wanted to draw out is the importance of the harm-benefit assessment which is part of the animal research legislation. This is also applicable the veterinary clinical research because if the harms are not outweighed by the benefits then it should be questioned whether you should be doing them.

He said that assuming all veterinarians were moral agents he wants to raise the question how do they decide what research is right to carry out? Is it simply a matter of legislation? Or are there many

gaps in the legislation where you have many individual ethical decisions being made? He thinks that the latter is true in veterinary practices.

He noted that, generally there are basically two ways to decide whether any action is right or wrong. We can take the fact that an action itself is wrong. Referring to the 10 commandments e.g. murder is a wrong action. The other way of deciding is to look at the anticipated outcome. So perhaps it doesn't matter what the action is, the benefits that come with that action. The terminology of the two is approaches:

Deontology: is the normative **ethical** theory that the morality of an action should be based on whether that action itself is right or wrong e.g. using a set of rules, rather than based on the consequences of the action. This refers to animal rights and persons holding this view believe it is always wrong to kill animals or to make them suffer.
Utilitarian view: Utilitarianism is an ethical theory that determines right from wrong by focusing on outcomes. This means that you can do anything to animals, with the caveat that harms must be balanced by benefits.

He noted that in practice you can find both rules and outcome based approaches: He noted some examples in ethics where people have had to assess the harm against the benefits (examples of killing one person to save 7; conundrum should one allow a father to give up his life to give his two kidneys to his two sons).

In general, even with strict rules a utilitarian analysis is also applied. Veterinarians are a special group, he explained, as they are assumed to work in the best interests of animals. It is even written down in various veterinary oaths and statements:

In the UK, veterinarians swear:"…my constant endeavour will be to ensure the welfare of animals committed to my care".

And in the American oath it says:
"Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society ***through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge.*** *I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics. I accept as a lifelong obligation the continual improvement of my professional knowledge and competence"*

He explained that he had added the bold part.

He added that for the group of lab animal veterinarians there is a bit of a dilemma as they have taken an oath to protect the welfare of animals and yet in experimental research we literally harm animals. Surely that is against the veterinary ethic of protecting animal welfare. And that is why, in his opinion, some of this is a personal ethical decision to get involved. For experimental research, the harm benefit analysis assessment is particularly important because by harming some animals, other animals also get some benefit from it (e.g. vaccine development).

He noted that there is an exemption in the research Directive for non-experimental clinical veterinary practices, so called in the UK "recognised veterinary practice". When thinking about some of the

talks from this conference, reporting research that is trying to advance veterinary knowledge (*pari-passu* it may also help someone obtain the diploma so it is often a mixture of both?). Secondly, an important question is whether the research being carried out is recognised veterinary practice or experimental research that needs to be licensed under the Directive? Regardless of the legislation, in both cases it is research, but the difference lies in the animals being used, clinical cases or naïve experimental animals. In both cases researchers are trying to answer important questions. An element of recognised veterinary practice therefore has to involve some experimental work to find an answer. He pointed out that 'experimental' means that you do not know the answer, which is why you are doing the research in the first place. That approach is independent of the animals being used.

He then referred to clinical veterinary trials where there is another exemption to the legislation. He noted that much of research in practices is outside the directive and causes no more harm than the normal treatment might do. In classical experimental research, the level of harm has to be licensed under the EU Directive if it is more than that caused by the "insertion of a needle in accordance with good veterinary practice". If it is clinical research work and exempted from the controls of the Directive, i.e. non-experimental veterinary clinical practices (or RVP), then more harm that that minimum level can be caused and it does not need to be licensed under the Directive.

My question is how is that work controlled and who decides it can be done?

In his opinion, there were many examples at this conference of veterinary clinical practice that involves experimental work. They would be covered by the term recognised veterinary practice.

He noted that Harry had mentioned that drugs used in the 'cascade systems' (old drugs new uses, etc). In these cases, it is important that the prescribing vet has something called "equipoise". That is when there are two alternatives to use, you truly do not know which one is better. Is the 'experimental' drug treatment going to improve things or make things worse. That is why you are carrying out this clinical research to help decide whether it is really advancing knowledge.

For clinical research or research on animals needing some form of treatment, the Royal College of Veterinary Surgeons in the UK looks at whether it can be classified as recognised veterinary practice or whether it should be covered by the Research Directive. In recognised veterinary practice it usually directly benefits the same animal and only indirectly others. That is not the true for classical experimental research, because that area involves the use of healthy naïve animals bred for research and those are important differences. There has to be a strong element of potential benefit for the animals in clinical research.

The following issues are some of which need to be scrutinized when an Ethics Committee is approving recognised veterinary practices. Animals are incompetent to make a decision about allowing research – they are like children and so the owner/keeper must consent on their behalf. That is why it is the prime duty of a vet to help the owner decide whether the research is in the best interests of the animal or other animals.

1. Has the owner consented in a valid manner? The vet needs to explain what will happen to the animals, what they have to do, what are the chances of success, what are the side effects of the drugs that may be important for that animal. So, it needs to be understandable, in lay language. If an owner decides not to consent and then that decision has be respected, even if the vet may not think it is the right decision.

2. It must be made clear that even if the owner has given consent, they can withdraw it at any time, e.g. if the owner feels unhappy for any reason. Furthermore, they can withdraw without any penalty to them or to their pets either now or in the future.
3. Is the project scientifically robust? Is it well designed - it would be unethical to carry out a project that was not scientifically robust. For example, as part of assessing the experimental design one needs to look at whether the statistics are sound? Are the exclusion and inclusion criteria for the selection of subjects valid, because they make an important difference to the test group. Have humane end-points been specified i.e. when to withdraw from the study and instigate rescue therapies.
4. The level of harm might be very important in the harm benefits assessment, because if you have small benefits, your harms also must be small. If you have considerable benefit, you can have higher harms, you could go from mild to moderate harm if the benefits likely to be gained are significantly large. It is therefore important be able to recognise and assess the level of harm being suffered by the animals. What are the clinical signs that the animal is showing that will lead you to conclude that an animal has gone from mild to moderate suffering? In this regard animals and humans are significantly different, because animals are like babies or children, they cannot tell you they are suffering - you must observe them to determine that level of suffering.
5. Are there any interim data that may indicate that the drug being tested, or the proposed treatment may actually be worse for the animal patient than the standard treatment you are comparing it with? (The control should not be a 'no drug' placebo but the standard best treatment available.)
6. Has the research been adequately funded? Will funding last the duration of the project?
7. What about the incentives and the compensation for the owner? Are clients being coerced into consenting to take part in this study e.g. by paying them over-generous expenses, or even providing free treatment? He outlined that this is a big problem in human research, because poorer people enrol for several research projects at the same time because they need money.
8. Is there an incidental findings policy? If you find something that was not expected, e.g. a tumour on an MRI, do you feed that back to the animal's owner?
9. Is the owner information sheet and is the consent form comprehensible to the lay person e.g. is it in that person's native language. Thinking about a human patient, a doctor would give the human patient several options and help the person decide (which is why it is better to have a separate person taking consent from the researcher or the patient's normal doctor). The doctor can provide advice, which is OK until the patient happens to be incompetent to make that decision, e.g. mentally handicapped. A further complication can be when a child is the research subject and the parents disagree? He noted that at that point, and there have been several cases recently, it had to be resolved by going to the Law Courts.
10. Is the data handling adequate? The GDPR enforces data protection regulations requiring that consent is obtained to use any personal data held or being used for the research which can be important for research involving clinical records.
11. Will the owner be informed of the results?

This gives you a quick idea of what is being looked at before approving an application for recognised veterinary practice.

At the end of his speech he noted that he wanted to leave the audience with a thought:

What are the morally relevant differences between animals and humans that justify different treatments? This is a question raised by Peter Singer, when he was looking at the human use of animals in classical research in relation to the use of other humans in research. You might say it is obvious, but what are the morally relevant differences between animals and humans that justify one and not the other? Is it the fact that humans are more intelligent than animals? If that is the reason, then why do we not use mentally retarded humans instead of animals? Is it because we **can** do it, because we are stronger? But is that a good moral way to go forward – might is right? And he agrees that this is a quite difficult question to answer to justify our current use of animals.

In reality we value both human beings and animals. Animals have an extrinsic value, which is their value to us, but animals themselves also have a value by virtue of themselves, a so-called intrinsic value - a value in their own right regardless of any extrinsic value or utility to us. And both those values have to be respected, as in humans.

So he said that he was going to rephrase the previous question. What is the morally relevant difference between a laboratory dog and pet dog that can justify different treatments? Is it because the lab dog is an orphan dog, who doesn't have parents, whereas a companion dog has owners who care for it? Is that the only difference, and if so is that a morally relevant difference? Or are there some other differences? Because this is a veterinary dilemma phrased in a slightly different way.

He asked about the audience's opinion. He added that they have heard about some non-animal experimental techniques, like *in vitro* work, use of computers, and evolving techniques such as genomics, proteomics, metabolonics, genetic profiling and so on. These are all good developments, but not true replacements – you cannot fully study pain in a test tube, you cannot study death of an overdose of anaesthetic in a test tube, you cannot fully study an immune reaction in a test tube, because for all these projects one needs the whole animal.

He thinks that the future is looking promising for replacements and is fast developing area for some areas of research, even replacing whole animals. There are now some very interesting data showing even more limitations to classical animal research. Even the high health and genetic fidelity of laboratory animals assumed to be so important, may now be misleading. In the past these variables have been accepted as essential for research animals and they still are, but in addition they do faithfully represent the human animal. We still have a lot to learn about the use of animals as models for humans in science.

The scientific basis for evidence-based veterinary medicine is an important challenge in terms of veterinary practice. He thinks that there are some roles here for ECVO to provide technical support for applicants using RVP and for clinical studies in general. ECVO are doing extremely well for financial support for clinical studies. However, he thinks that the ECVO has a moral responsibility to approve research that is done in with College financial support from an ethical viewpoint as well as from a scientific viewpoint.

He closed his speech.

Charlotte Keller introduced the third speaker, **Dr Gill McLellan.**

Dr McLellan graduated in 1990 from the University of Glasgow Veterinary School. After a few years spent working in general veterinary practice, she gained her first qualification in veterinary ophthalmology in 1993. She then completed a residency and PhD at the Royal Veterinary College, University of London. Dr McLellan moved to the USA in 2000 and has since held faculty positions at UC Davis in California, Iowa State University, and the University of Wisconsin-Madison. Currently, Dr McLellan holds positions in both the School of Medicine and Public Health and the School of Veterinary Medicine at UW-Madison. Dr McLellan is board-certified in veterinary ophthalmology by the Royal College of Veterinary Surgeons in the UK, the European College of Veterinary Ophthalmologists and the American College of Veterinary Ophthalmologists. She is Past-President of ECVO. She is on the editorial board of the journal of *Veterinary Ophthalmology*, and also serves as a Member of the ARVO Animals in Research Committee.

Responsibilities of veterinary ophthalmologists in veterinary clinical and biomedical research
(Gillian McLellan)

Dr Gill McLellan thanked Harry and David for presenting these issues and she was going to try to tie them together in terms of how they really affect us as veterinary ophthalmologists in terms of our role in both clinical and biomedical research. She mentioned that she has no financial relationships to disclose.

So obviously as a vet ophthalmologist, you have a somewhat unique perspective on vision research: that of a clinician and often times as a clinical scientist, or as a basic scientist, many are engaged in some kind of research as we see in presentations at the conference. We don't tend to think in terms of degrees of sentience because regardless of the species presented to us, whether gecko, pigeon, dog or cat, they are all our patients. So, the veterinary ophthalmologist engaged in animal research is confronted daily with the veterinarians dilemma when considering animals from a research perspective.

She asked "what the motivation of this discussion really is?" She states that she would also refer to the oaths, David had already mentioned, and she had originally started with the Royal College of Veterinary Surgeons', but noted that she was particularly struck by the American Veterinary Medical Association's oath which really captures the tension that certainly many experience every day in their clinical and in their research roles.

"Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills ***for the benefit of society*** *through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources,* ***the promotion of public health,*** *and the advancement of medical knowledge.*

I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics.

I accept as a lifelong obligation the continual improvement of my professional knowledge and competence"

Focusing on the phrase "for the benefit of society" she noted that this was an overarching theme, that David did not really mention, that incorporates the benefits for society as a whole and which returns to the content of the previous slide, addressing "One Health", because we vets can contribute not just to animal health but to the wellbeing of animals and humans globally.

We want to accomplish that " *through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources"* – and she added that certainly they have a role to play for example in the understanding of the genetic basis of inherited retinal diseases that cause blindness in species that maybe endangered, or may even be facing extinction and may have a very small gene pool.

The conservation of animal resources may also involve how to maximise the health of animals from a herd perspective as well. The promotion of public health is critically important but she does not want to address in detail because she thinks everybody is aware about the massive advancements for human health that have been accomplished through clinical and basic veterinary research and the advancement of medical knowledge that has ensued.

Referring to*: "I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics."* She noted that at the AGM, the day before there was a discussion about how grey the area of ethics really is.

But she thinks that what they really have as vet ophthalmologists, is a real responsibility for thoughtful and active engagement which is why she is thrilled this forum is being held. Everyone exists in this state of tension, being pulled in different directions according to the national oaths they have taken. But they also occupy different spaces and, indeed they don't often occupy the same moral or personal space from hour to hour, from day to day, they may feel differently about things on different days and different times and under different circumstances. In her opinion, vets must advocate for animal health and welfare. She shows a picture of a French bulldog, which is has become one of the leading breeds in the UK. They are adorable dogs, but this is a real moral and ethical dilemma for the veterinary profession. Most of the patients that they see as veterinary ophthalmologists are produced that way - they are wilfully generated genetic mutants and the fact that they deal with these animals as patients, and these efforts effectively pay our bills – introduces an ethical conflict. This, again, puts us in a state of tension, presenting a moral and ethical dilemma in our daily career.
Clearly, they want to pursue advancements and improvements in clinical care for their veterinary patients and also, for those involved in biomedical research, for human patients as well. She noted that one of the things that drew her to veterinary ophthalmology was the true comparative aspect and how engaged and involved veterinarians have been in research that may benefit humans. But they can also be responsible in a smaller component for the conduct of research: they may be recruited for expertise in toxicology studies and may be, indeed should be, involved in the oversight of those studies. And also the oversight of the nature of the clinical studies that they themselves may do in a clinical setting. She thinks that public education, both in terms of advocating responsible animal research and advocating for responsible animal ownership and for responsible animal breeding is a moral imperative for vets.

So the role of vets can lie anywhere on the translational spectrum: from basic research, dealing with test tubes, pipettes and stuff in the lab at a molecular and cellular level, all the way through basic research involving animals and preclinical studies, e.g. looking at toxicology and tolerability of new treatments, and clinical veterinary medicine and also the application of new medicines and therapies to human patients.
She shows the picture of "Lancelot" which was a now-famous dog in an RPE 65 gene therapy study that is credited with saving the trajectory of gene therapy for human diseases and proved instrumental in the development of the first FDA approved gene therapy for retinal degeneration in

human patients. This is something that has promise to restore vision to children and that story may not have been possible without the efforts of veterinary ophthalmologists like Kristina Narfström and Gus Aguirre. It is always easier to justify some of these studies when researchers meet e.g. the parents of children that are blind or losing their vision and reinforces this as an example of a way in which vet ophthalmologists can contribute to human health.

But what is very important is that when veterinarians are involved in any aspect of the translational spectrum, regardless of whether it is in their clinic or in a lab, that they follow the principles that David alluded to for study design and for the responsible conduct of the research and also ensure the oversight and, to be addressed later, timely reporting and dissemination of findings.

She asked the audience how many of them has read the ARVO Statement on the use of Animals in Ophthalmic and Vision Research (she mentioned that it was impressive that probably more than ten people raised their hands) then she asked how many people in the audience have submitted a paper to the journal, "Veterinary Ophthalmology" (she noted that a few more hands were raised for the latter).

When you submit a paper to the JVO, you check a little box that you comply with the ARVO Statement on the Use of Animals in Ophthalmic and Vision research. So, she had thought that this would be a good way to ensure that people are conducting research in a well-defined manner because it is a fairly good and useful statement. However, once she joined the ARVO Animals in Research Committee and when she had read it "properly", it became clear that this statement perhaps does not apply very readily to aspects of clinical veterinary research. It is really designed to serve as a guide for those who are using experimentally-induced animal models of disease, so it does not actually really apply to vet ophthalmologists, although there are aspects that would be benefit for them to consider.

The number one thing is that they should avoid using animals when possible, and that is the number one thing in the statement, because *if there is an alternative, you have to use it.*
They need to apply the principles of the 3Rs, they need to reduce the number of animals, they need to refine the use of animals and we need find replacements for the use of animals whenever possible.

At this point, everybody should really stop and think when you are conducting a study, whether it is in your clinic, trying something new out in your patients, or whether you are being asked by a colleague at a medical school to do a study: Are they really relevant to animal health and to human health and are there alternatives?

She noted that she herself is doing about 3% of the studies she is asked to do or that are suggested to her by colleagues and that is based on her own moral and ethical judgment. Not necessarily because the suggestions were bad science, but there just may have been better ways to do it that did not involve using animals, or that other steps should be involved before animals are involved.
We need to consider things like sex as a biological variable, and in a clinical retrospective study this might be something that is difficult to do, but many studies that are done in laboratory animals are using animals of a single sex - it is questionable if this going to be valid. Strain differences, as David alluded to, can be important too.

She noted that they should minimize (and she gave her personal opinion that they should really avoid) discomfort, distress and pain; stressing the importance of pre-emptive anaesthesia and analgesia when they do studies in experimental models.

Moving on in the ARVO statement she noted that there is a section that mentions specific factors that should be considered that are very specific to studies that are related to vision and ophthalmic research.
One of these factors is that if your studies may or will produce visual disability (and ARVO's definition of visual disability is: "sufficient to impair physiological and physical functions") that is, to paraphrase, a "big deal". This would be applicable to studies in an experimental setting or maybe even if a clinician is trying a new surgical treatment that has not been tested before, and that is something that frequently has not been considered by researchers who claim that they are in compliance with the statement.

Now, how "big a deal" the visual compromise is for the animal likely depends very much on the species, and they as ophthalmologists should be in a good position to make that distinction. She noted that actually many mice are blind in laboratory settings because they often are strains that carry mutations associated with retinal degeneration that can confound the research but it doesn't have a huge impact on the physical and physiological wellbeing of those nocturnal species, with whiskers, in a small cage. However, it may be more of an issue for species like a nonhuman primate if the experimental procedure or intervention elicits blindness: they have apposable thumbs, they usually sit and look and things and poke around with things, they watch TV from their cages even, so eliciting blindness in non-human primates, regardless of your feelings about research involving these species, is a bad thing.
We also need to consider what is the validity of using the contralateral eye as a control? There is a lot of controversy surrounding this at the moment in basic research circles, because many things that you can do in one eye may impact immune responses in the contralateral eye, for example, and may actually impact what should be your control. This may actually require that you use more animals so that you have naïve controls, rather than using the untreated eye of a tested animal as a control.
So, if you are going to do bilateral ocular procedures, you have to have a really very strong rationale for doing that.

Something she doesn't think vets are very good at is, especially in basic science, is reporting and documenting adverse events, e.g. how many subjects in a clinical study did not respond or got worse as a result of the treatment. That tends to be swept under the carpet and we need to do a better job about this.

For those of us who work with animal models in which we are specifically breeding animals, which might be abnormal, we need to make the best efforts that we can to share those resources, which is actually an imperative that is documented in the ARVO statement.

The problem with the ARVO statement is that it actually does not capture some of those problems that veterinarians, and veterinary ophthalmologists in particular, might have with clinical studies. How do these things really apply or whether they don't apply really clearly to someone in practice, conducting clinical research.

She drew the attention of the audience to a paper that was published in the ILAR Journal. [Baneux, PJR et al (2014) ILAR Journal, Volume 55, Number 1, doi: 10.1093/ilar/ilu005]

This paper actually goes over in quite a lot of detail some of the issues that a related to conducting clinical trials involving privately owned animals, which applies to many veterinary ophthalmologists. She shows a flowchart that is taken from this paper and essentially this is a model that is used in some Colleges of Veterinary Medicine, e.g. Cornell, University of Wisconsin-Madison, or The Ohio State University, where there is a two tiered review mechanism and essentially you think about:
Is your research involving tissues that are being taken anyway from animals and you are not taking extra tissues or extra samples beyond what you would normally take under general practice standards from those animals? Then, you probably don't need to have independent approval but it would be a good idea to ensure you have consent of the owner still.

Are you going to subject an animal to a procedure that wouldn't normally be part of your clinical practice? e.g. you are testing a new surgery, that has not been demonstrated to be effective, then you going to need some oversight, whether it is going to be clinical oversight from a clinical review committee (that you generally are not going to have in most private veterinary practices) or an institutional animal care and use committee, or even federal or national oversight and compliance.
So she would really encourage the vets to review this flowchart and she thinks that this is probably something ECVO should consider because other organisations are already pursuing this.
She thinks that it is imperative that there is a review mechanism in place for veterinary practitioners.

So essentially, she has gone over the roles in research and she thinks that additionally what is really important here is timely reporting and dissemination; how to report our negative results, which can be very challenging; and reporting to ensure rigor and reproducibility, i.e. so that someone will be able to replicate the results.

She also wants to draw the attention to the ARRIVE guidelines (Animal Research Reporting of in-vivo Experiments), which she thinks could be something that is more valuable perhaps than the ARVO statement on the Use of Animals in Ophthalmic and Vision Research, for ECVO members and trainees to take on board. These guidelines were developed by the National Centre for the 3Rs in the UK. It essentially provides a checklist of 20 items which she thinks would be great for all reviewers engaged in the editorial process and the peer review process for veterinary journals to follow these guidelines and to have a checklist and also, as authors composing new manuscripts to consider and incorporate all those applicable items that are on that check list in terms of study design, experimental protocol, any adverse events etc.

She closes by saying that really, they can do better, they are doing great but the current climate and to given their own tensions - everyone should be doing the best job that they can.

Charlotte Keller introduced the fourth and final speaker, **Dr Jane Sansom**.

Dr Sansom who graduated from Bristol, worked in private practice for 10 years, then specialised in ophthalmology, working at the Animal Health Trust as Head of the Unit of Comparative Ophthalmology.

Have we done enough?

(Jane Sansom)

She challenged everybody at ECVO to re-think the use of animals in research.

She noted that the questions that are often asked in relation to the use of live animals in experimental research particularly invasive research was whether the research was ethically justifiable. She added that a very good book had just been published by Andrew and Clair Linzey from the University of Oxford "The Ethical Case Against Animal Experiments", with two veterinary contributors, one of them was a past professor of medicine in veterinary science, a member of ACVO and a research worker.

She noted that the other question that was often asked of research, was whether it had value or utility in terms of significantly advancing our scientific knowledge in a manner that could not be obtained by any other means.
She added Harry that had already mentioned that there were now alternative animal free technologies that should and could be considered.
She noted that some of you are already going down this route and that hopefully these would become the methodologies of the future.

She stated that underpinning research is economics and perhaps the moral justification for this type of research should lie with those who fund it.

For those of us who have worked with research animals it did pose an ethical dilemma, but we have always managed to square it in our heads that we are doing the very best for the animals under our care. However, she posed the question as to whether we should be doing more than just care and welfare?

She suggested that we should be ensuring that the animals that we were responsible for should have a life that is worth living and a life that is worth living to them.
She added that with some justification, unfortunately, we are often described as "Jekyll and Hyde profession", as we transition from caring for an animal in the consulting room to killing that same animal in a laboratory.
Is that not a contradiction?

She noted that this change of mindset, this disconnect between the heart and the head, some would say it is pathological not only occurs on an individual level but on an institutional scale and that is frightening.
We manage to normalise, what otherwise would be regarded as unacceptable and sometimes abhorrent practices and this applies to at least 115 million animals stuck in laboratories worldwide.

She stated that the utility for using animals in research has been questioned.
Some would say that the benefits of this type of research have been overemphasized.
There are some well-respected scientist saying that there is a lot of bad research done for the wrong reasons. Bad research because animal models are not predictive for human disease they cannot be.
You can use them to speculate or test a hypothesis.
If they were predictive there would be no need for clinical trials.

For example in toxicology, 92% of clinical trials fail for drugs that have already been ”safely” tested on one animal or probably two animals. That is because these drugs are ineffective or they have side-effects when it comes to their use in humans.

She added that although it seemed counter-intuitive, the use of animal models that are genetically similar to us has not delivered the advantages they should have done. This brings us to the very tragic situation of the use of the Great Apes. For over forty to fifty years they have been subjected to experimental procedures in less than ideal conditions.
A systematic review of the data, which is not often done, had demonstrated that this type of research was unjustified, uneconomical and above all unethical.

She then referred to the ECVO as being no different to any other specialist discipline in relying on the legislation of the country of origin and the ARVO guidelines to try and ensure a uniform level of protection for research animals. Unfortunately, there is no over-arching international legislation, so there is no uniformity in the protection provided and you have to remember that some countries have no concept of harm and some cultures have no concept of animal consciousness. She added an example of this was a publication in 2013, in the Journal of International Surgical Neurology.
This was publication was sadly and unfortunately titled “Heaven”. She explained that this stands for “Head Anastomosis Venture” - in other words, head transplants. She noted that she had no problem with people transplanting their heads with consent but for animals it was a living hell. This type or research had been going on for a hundred years and it would continue to go on because nobody has the power to stop it other than perhaps public opinion. She added that public opinion, as we have seen in recent times, could be very persuasive.

She stated that we need research, we need good research, we need it to be transparent, to avoid pain and suffering and to be productive, but above all we need it to be ethical. If we performed studies that were underpowered or under-resourced, they would be regarded as unethical.

An example of this was in the Journal of *Veterinary Ophthalmology* in 2017, where there was a study describing the application of a toxic drug to the eyes of 30 animals. Unfortunately this study was underfunded. There was a succession of problems. The appropriate samples could not be collected. The appropriate biochemical assays could not be conducted. When it came to histopathology, only three out of 30 kidneys were examined. All you could say about this publication was that the author had been extremely honest. Reviewing the literature, it had been shown that the model the author had chosen was unreliable.

She commented that if we published studies like this, we are merely encouraging more of the same and you had to ask: What happened to the ethical oversight of this project and what happened to publication ethics?

She noted that there are also studies that were repetitive - at ECVO in 2014 and 2015 there were two very similar poster presentations by some of the same authors, describing the creation of scleral outflow channels in the eyes of experimental dogs. This was to demonstrate a reduction in intraocular pressure. The contralateral eye of some of the dogs had the intraocular pressure artificially elevated with an infusion of saline. She questioned why we had to repeat these studies that are visually impairing and painful ?

She added that in her opinion, there were also studies where the value of the research was not proportionate to the animal suffering. In 2016 at ECVO there was a poster describing enucleation in two animals. One eye from each animal was removed to confirm the presence of retinal dysplasia, which was exactly what it did. There was nothing to suggest that the retinal dysplasia was in any way atypical or interfering with the vision. So you have to ask why would not ophthalmoscopy have sufficed?

She then stated the final example was in a paper in the Journal of *Veterinary Ophthalmology* from 2009, which described a cosmetic study to compare enucleation with various types of intraorbital prosthesis. 18 healthy dogs had one normal eye enucleated or eviscerated with the placement of an implant .

She asked: "What are we doing, as veterinary ophthalmologists, taking healthy eyes out of healthy dogs?"

What are we doing performing these types of studies for cosmetic purposes?

What is published in the literature, represented us all.

She asked the audience whether this type of study represented their professional ethical values? And stated that it did not represent hers.

She noted that doing research was a choice, using animals in research was a choice and ECVO had a choice.
She stated that we can continue to do things the way we have always done them and that would be the easy option, but she believed that in the not too distant future we would look back and wonder why we had been complicit with so much suffering.
Or we could draw a line under invasive live animal experimentation.
She believed that this would be more in tune with public opinion, more in tune with membership views and more in tune with forward-looking scientists.
Remarking that we could not turn back time, but hoped many of you would have the opportunity, with a bit of courage, to carve out an ethical future.

She closed her speech in thanking Claudio Peruccio for allowing her to raise this contentious issue, thanking Peter Bedford, Charlotte Keller and the ECVO Committees to having foresight to arrange the session today. Thanked the audience for listening.

Discussion

Charlotte Keller thanked everybody for their contribution. She invited questions.

Sheila Crispin:
"Thank you very much for stimulating discussion. All I wanted to say is that next time, please can we have that as part of the main conference, because it is so important.

Thank you very much for all the contributions, which were provoking, which is always good. I also want to go one step back, as those in the UK know - we have made a very sad decision to leave the EU, and we are having some difficulties transposing EU law into UK law. One of the things that has been difficult is the transposition of our animal sentience. Let us define 'Animal' - do we just mean vertebrates or do we mean 99% of the animal kingdom that is invertebrates? Do we then define 'sentience'? As Jane mentioned yesterday, it is all very good to says that we are ethical but then you have to define that as well. So I think we have to move forward, we have some really basic definitions that we have to define and then we can start moving forward as we must, because these are really important matters and just as a final fling, those of you who haven't read it buy it and read it: "The secret life of cows" because that makes you think and that what it is all about - making people think and not just adopting a routine that actually may be very harmful to you later on in life when you think I really should not have done that, but also to the animals to which you have done it. Thank you.

Comment: Thank you to all the speakers. I guess yesterday, at the AGM, the question was raised how can we assess this issue, because one of the reasons why we are discussing this within ECVO is how do we select our abstracts and the difficulty with this process, so how can we avoid the issues that actually brought all of this conversation, so is there a way that we can try and select and chose or a guideline because clearly as still said, the ARVO statement does not apply to many of the clinical research that is reported at the ECVO meeting, so maybe we need a guideline for the authors focused on more clinical researches that can abide and follow an ethical approval form from ECVO or from a combination of ECVO and ACVO to the clinical researchers can abide.

Jane Sansom: I agree with Marian's comments and ask Harry and David to help out because I am not a research worker, but I get the impression that the legislation is weak, it is full of holes. We accept research from different parts of the world but there appears to be no uniform ethical code of practice.
I do not see why at ECVO we could not have our own ethical code of practice to try and address some of these 'loop holes'. We don't just see problems in invasive research, where obviously most of the harm is done, I see problems with non-invasive research.
We need to question why we are doing this study? We see repetitive studies on Schirmer tear test and intraocular pressures. We are now capturing animals from the wild to measure their Schirmer tear tests – is that ethical? Do we really need to know the Schirmer Tear Test readings in a Caiman and do what I would call "pick n' mix" studies with a variety of species. Is that good research?

Harry Blom: I agree that there is a true need for a, let's say, global legislation that makes sure that all countries are conducting animal experiments, if to be conducted, under the same standards. What I have expressed is the regulations that we have presently in European Union, which are I think possible the most strict available on the globe if you compare it, for example, to the American situation. Not all species that are covered by the Directive are covered by the American Law on animal experimentation, although there are differences between NIH funded research and other research, but the ARRIVE guidelines, which are not a legislation, can be used on a global level to assess animal experiments and also decide to have them presented for that instant in this conference. That would be a good way forward, although difficult, but a good way forward and a starting point.

David Morton: An interesting point from Sheila [Crispin] was: Why is the UK animal welfare legislation so far ahead of the EU legislation in welfare terms despite the fact we did not have sentience? That is a question.
I have talked to several multi-nationals, which have the same problem regarding the so-called national viewpoint of what is acceptable and what is not. And the advice I give them is to set your own standards. Simply because it is cheaper to do some work in China or Singapore than in America or somewhere in Europe, you have to live by the standard you set and the work that you fund and that is where I think is the ECVO should go and have some sort of scrutiny of the proposal that you support, because there is a mixed field out there, and it would take ages to get everybody set up a world standard and of course nobody will agree on a world standard. That is the practicability - they can't even agree on a nuclear disarmament. But what you can do today is to set your own standards and stick with those and I think the ECVO [standard] is generally good, but you know it is the details. You have some very broad principles and it is how you apply them. You can talk about minimal harm for example, as they do in the US, we can talk about mild severity – but how do you recognise what is mild to an animal, ok for pain perhaps, but what about distress? We talk about removing the eye of an animal – how much pain and distress does this bring to an animal?
Consider so-called blind model animals – kittens, that you made blind from the time of birth and you could not have told they were blind ,they weren't distressed at all. You cannot really tell at all. It is really a problem of recognition of animal suffering.

Harry Blom: There is also a problematic situation because many species, especially the prey species, do not even show that they are suffering from discomfort, because that is not relevant to them - they don't do it in nature, because that would show weakness, and so they don't do it in the laboratory as well.

Jane Sansom: I think it raises the question again, which I have already raised, whether we should be doing this type of work and how many of you feel that it is appropriate as veterinary surgeons that we are inflicting what David has already said which would be regarded as cruel if done anywhere else other than under experimental "research". You would be breaking the law because these are cruel practices and yet we endorse them under the name of "research".
Along with that, the language tends to reduce the effect. You don't talk of "brain damaged animals" – you talk of "naïve animals" you don't talk of" blind animals", you talk of "blue models". There is a whole institutional way of dealing with this problem and as it has been said, we need to de-normalize and de-institutionalise these practices.

Charlotte Dawson: Thank you very much - it has definitely been a very thought-provoking session, which I am very pleased that we had today. I am from the RVC and am UK based and I just wanted to explain a little bit about how our ethics and welfare committee also judges clinical research.
I apologise that today our studies did not include the ethical approval number, but they certainly did have that and you know that apart from the study the ones were retrospective, so including retrospective research we have to have ethical approval before we can undertake any study and it might be a little bit confusing why you need an ethical approval for a retrospective study but it includes all the things that were discussed including data protection, which I think is very important too. So I propose that we actually have some form of ECVO guidelines related to experimental which would fall under probably under the ARVO guidelines but we come up with some sort of clinical research ethical code that we could then implement and follow – that would be my suggestion.
Thank you.

David Morton: There is another set of guidelines coming forward, called the "PREPARE guidelines", which put a lot of flesh on the ARRIVE guidelines, these are actually, I think better. For example, ARRIVE guidelines to not mention humane end-points, which I think is a tragedy, but PREPARE guidelines do - so look at them both.

Jane Sansom asked David Morton: You mentioned the morally relevant differences between animals and humans. How would you answer that?

David Morton answers: That has been the subject of many papers, for example what are the morally relevant differences between a mentally retarded child and a chimpanzee? You have one group like the Peter Singer Group saying that if you can't use one, you shouldn't use either, and then the Ray Frye camp who say you should use both. So when you get to the end of the ethical discourse, you are left with this sort of option – you have to choose a chimpanzee or a mentally retarded child because from an intelligence viewpoint there is no difference. So I think the question is that you should use neither probably, which is what the Americans have just come to agree. After years and years of using chimpanzees, they had an ethical committee which looked a chimpanzees and decided for the reasons you said that very little uses come out of the chimpanzee experiments so they eventually decided not support the use of chimpanzee in research – they are the closest relatives, but it is still taking a very narrow view, we do not know how animals suffer and we do not know what that in terms of live experience. So it is all a philosophical conundrum how to deal with that one.

Jane Sansom: Again, because we cannot answer that question, should we not give them the benefit of the doubt and say we should not use animals in invasive experiments?

David Morton: It is Pascal's dilemma which says you have to believe in god because that is the safer thing to do, whereas if you don't believe there is a god and there is one you go to hell but if you do believe in god and there is none. So, Pascal's moral dilemma is the same as in animal research. It is probably better not to do it but then, you have to say, on the other side of the scales – where would we be without animal research? Without rabies vaccination – many of people died of rabies, we have the impact of vaccination plus hygiene, that has actually made an enormous difference to the quality of life of humans. Jane's point is an interesting one, it is a relevant one, well ok, put that to one side now, this is where we are - what are the benefits from where we are going forwards on animals with the advent of the genomics etc. It is a changing scene and we can now do without a lot of animals which we could not done before because our knowledge has increased, so it is time to look again and look forward – I completely agree with that. But don't let us say that all animal research in the past was of no benefit - some was of enormous benefit.

Jane Sansom: I agree with that comment, but it has come with an enormous cost to animals and a lot of the research may not even be published - we don't know the costs in terms of harm and suffering.

David Morton: And don't forget there were experiments on humans back in the clinics and slaves were used as experimental subjects, so we have a chequered history.

Jane Sansom: Yes, and they were regarded as morally acceptable at that time and morality changes, it is always further along the road than it is practised.

Harry Blom: But I think it is a task of both the scientist and the scientific journals to make a mindshift to allow and to promote the publication of negative results, because at the moment, the scientist is

probably unaware that there are possibilities - only a few journals allow negative results to be published to prevent that studies being repeated without any expectation at all.

David Morton: And in addition to that, I wrote a paper back in 1993, so you should not only publish negative results but also negative technology, so e.g. you tried something and it did not work and there is no place for that at the moment, but I think now with the internet and websites there is now a place for that, because whenever I raised that it was answered there is no room for this in journals, we can't put all this extra information in. But I think we are morally obliged to put in this information to find a place for it, which I think using the web could be an option.

Harry Blom: And something else that we see at the moment, is that fortunately the numbers of animals being used is still going down and at the same time the number of data generated in scientific articles per animal has much increased so science has improved but of course it is still not zero but there is at least a way forward and that is an important one I think.

Peter Bedford: There is an aspect that we have not raised today and I think it is important that we do: I worked for an academic institution for about 40 years and as head of department I felt the pressure to do research. It is incumbent for academics to do research because the existence of the institution is reliant upon research funding. That is how we grade and judge academic institutions in the UK, and I am certain it is true for the rest of the world. You have to produce your research and I am certain that some of the points that Jane raised about repetitious work, insignificant work, is all due to the fact that young people coming into academia are pressurized into doing research. I think we have to be honest about this and at the end of the day of course, that is all about funding, that is all about money. I feel sometimes that the legislation that exists is an excuse for these things to happen and we can do that because the legislation exists it gives us a right to do it – and I think sometimes I have done things perhaps in the name of research which were just not justifiable but as a result of pressure to produce publications because of the research factor. Thank you.

Jane Sansom: I agree with what you said entirely, it is referred to "publish or perish", a perverse scientific culture but there are people in this room that can change those perverse influences, they have the power to change things in academia. This may be pertinent for younger members coming through who do not feel an obligation to go down that route and can raise their concerns.

Harry Blom: Actually whilst serving at the University of Utrecht and the University Medical Hospital, both Boards have decided last year or even the year before that the quality of publications is prior to the quantity of publications and that is a general development now in the Netherlands starting in Utrecht and growing over the country – that is a good development.

Peter Bedford: Yes, that is good, that is a good development.

David Morton: Just quickly, I think the other thing is that the legislation is misinterpreted by other groups so the legislation says we want proof of safety and they interpreted that as carrying out animal tests – so sometimes it is the implementation of the legislation that is at fault, not necessarily the legislation itself but then people go on and say this is required, that is required.
I pick up you point, completely about academics having to bring funds to the university and the young people "publish or perish" that is why we are seeing not more fraud, you had no way of knowing the fraud level we have seen before because we now have better methods to find out plagiarism and so on. Absolutely right.

Charlotte Keller thanked the speakers for their contribution, and gave them each a gift, and thanked everybody for attending. She then closed the forum.
