Research ethics at the University of Liverpool

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Content

- What is an ethical approach and why is it important?
- Basis of modern research ethics
- Considerations specific to veterinary projects
- Application process (UoL)

Should humans be allowed to eat farmed sheep and cows?

Yes as much as they like **(A)**

Yes in moderation **(B)**

No **(C)**

Should humans be allowed to eat farmed sheep and cows?

(A) Yes as much as they like

0%

(B) Yes in moderation

0%

(C) No

0%

Should humans be allowed to eat farmed sheep and cows?

(A) Yes as much as they like

0%

(B) Yes in moderation

0%

(C) No

0%

Should humans be allowed to eat farmed Octopus?

- Yes as much as they like
- Yes in moderation
- No

Should humans be allowed to eat farmed Octopus?

Yes as much as they like

Yes in moderation

No

Should humans be allowed to eat wild Octopus?

- Yes as much as they like
- Yes, in moderation
- No

Should humans be allowed to eat wild Octopus?

Yes as much as they like

Yes, in moderation

No

Should humans be allowed to eat wild Octopus?

Yes as much as they like

Yes, in moderation

No

Is it always wrong to kill someone?

Yes

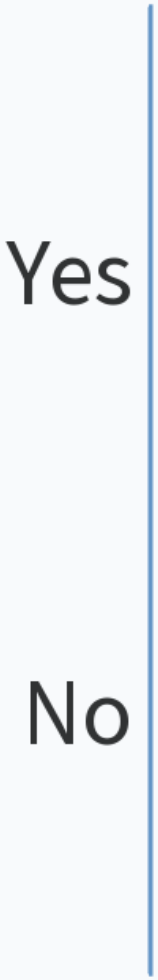
No

Is it always wrong to kill someone?

Yes

No

Is it always wrong to kill someone?



Should euthanasia for be allowed for terminally ill humans?

- Yes as their discretion
- No
- Yes, with some safeguards

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What is an ethical approach?

Laws

- Based on broad agreement on core 'norms' held by society
- Opinion on specific issues varies based on a variety of factors
    - Societal background, religion, experience

Cultural norms

- Factors outside the laws which may reflect acceptable ranges of activity and behaviour

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Cultural norms

- Factors outside the laws which may reflect acceptable ranges of activity and behaviour

Sometimes cultural norms change and lead to changes in laws

Why is an ethical approach important in research?

- An approach in line with societal norms:

1. Promotes good research behaviour
   - Knowledge, truth and avoidance of error
2. Promotes values essential to collaborative research
   - Trust, accountability, mutual respect and fairness
3. Promotes accountability to society at large
   - e.g. funders and more broadly public
4. Promotes public support for research
5. Promotes moral and social values
   - Social responsibility, human rights, animal welfare, compliance with law

Basis of a code of ethics

- Most organizations involved in research have a code of ethics
- These are often based on the:
  - Nuremberg code
  - Declarations of Geneva and subsequently Helsinki
- University of Liverpool has a code of ethics based on these documents

Nuremberg code

1. Required is the voluntary, **well-informed, understanding consent** of the human subject in a full legal capacity.
2. The experiment should aim at **positive results for society** that cannot be procured in some other way.
3. It should be **based on previous knowledge** (like, an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that **avoids unnecessary physical and mental suffering** and injuries.
5. It should **not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.**
6. The **risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits**.
7. Preparations and facilities must be provided that **adequately protect the subjects** against the experiment's risks.
8. The **staff who conduct or take part in the experiment must be fully trained** and scientifically qualified.
9. The human **subjects must be free to immediately quit the experiment at any point** when they feel physically or mentally unable to go on.
10. Likewise, the medical staff **must stop the experiment at any point when they observe that continuation would be dangerous**.

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Failure to meet ethical standards can have significant impacts on individuals or groups

- Lack of informed consent
  - Human radiation experiments
  - https://en.wikipedia.org/wiki/Human_radiation_experiments
  - Creation of first cell line HeLa – Henrietta Lacks
  - https://en.wikipedia.org/wiki/HeLa
- Withholding standard care
  - Tuskegee syphilis experiment
  - https://en.wikipedia.org/wiki/Tuskegee_syphilis_experiment
- Further examples
  - https://en.wikipedia.org/wiki/List_of_medical_ethics_cases

In what circumstance should research be done on animals for human benefit?

Top

Animal research - Brief history of ethics and legislation

- Bible - Starting point of animal rights

'God made man in his image and gave him dominion over all other creatures'

- 1780 – Barrister - Jeremy Bentham

'What "insuperable line" prevents humans from extending moral regard to animals?'

- 1859 – Darwin – Evolution
  - Humans are not divinely different
  - Animals may teach us about humans
  - Emotional continuum between animals and humans?
- 1876 – Animal cruelty act
- 1970 – Singer – Total good that results from research, must be balanced against suffering caused by the process
- 1986 – Animal in Scientific Procedures Act
- Ongoing – How much can animals suffer? Is their pain like ours? Can they be deprived of interests and desires?

3 R's of animal research

- Reduction
- Replacement
- Refinement

- Think of a situation where these apply in veterinary research? In what situations?

The need for ethical approval

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Staff and students

Research ethics policy

Veterinary surgeons and veterinary nurses

RCVS SETTING VETERINARY STANDARDS

Professional Code

All research projects should consider whether they require ethical approval or a home office licence **PRIOR** to being started

SUBMIT EARLY!

Benefit vs risk / harm assessment

Possible benefits

- Applications must demonstrate the research question is of value.

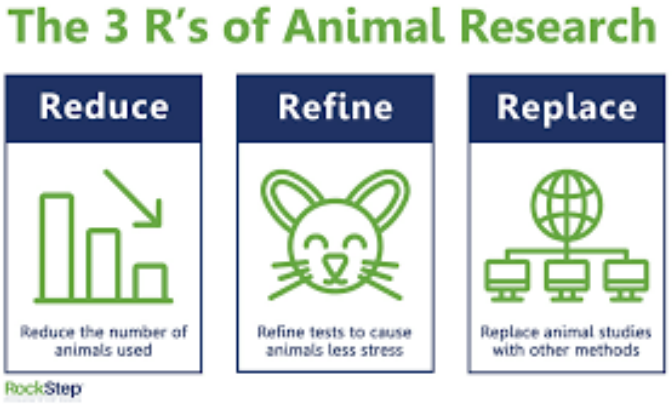
- Be clear and explicit about potential impact
  - Impact
    - Who could benefit?
    - What benefits could the outcomes bring?
      - **<u>Most research is incremental</u>**
      - A lot of research answers part of a question or a question in a context

Benefit vs risk / harm assessment

Potential harms

- Applications must demonstrate the risks have been considered and mitigated

- Risk / harms
  - Who / what could be harmed?
    - Consider human participants, animal subjects, researchers, society and environment
  - What harms could occur and how likely are they?
    - Vast majority of studies carry some risks



- Risk / harm mitigation
  - Power calculations for prospective studies
  - Is the method proposed the least invasive available?
  - Alternative methods elsewhere?
  - Participants / subjects involved in more than one project
  - Sources or support / distress protocols

Good study design important

- *Unethical* to carry out studies which cannot reasonably be expected to produce useful results, but carry a risk of harm

- Can you show support for your proposed work?
  - Patient involvement panels
  - Prior literature (peer reviewed or otherwise)
  - Funding
  - Supervisor approval
  - Peer review
    - Often quicker and easier than back and forth with committee

Informed consent

Participants should have an opportunity to consider the options

- Appropriate time to consider
- Opportunity to ask questions

Understanding and competence to consent

- Are the participants to make a decision and in a sound state of mind to do so?
  - Can the potential participants understand the information?
  - Can they rationalize a decision to participate

- Need to consider vulnerable characteristics in particular
  - Circumstances may make people vulnerable

Consent – The Decision

- Should be voluntary (opt in)
  - Are the potential participants legally and morally able to make this decision?
    - Are they the correct person to ask?
    - If there are multiple stakeholders encourage discussion between them
- Is it truly voluntary, competent and without coercion

Who should decide what level benefit is necessary to justify the risk or harm to the participants or animal subjects

Top

Access to research ethics review

Committees

- Universities
- RCVS ethical review panel
- Some companies and other institutions

- Usually there is cross recognition of ethical approval

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Research ethics in a veterinary setting

- BVA / RCVS report on research ethics 2013 discusses research ethics in the context of:
  - the unique responsibilities of a veterinary professional
  - unique legal issues relating to veterinary research

- Considerations for the veterinary researcher
  - Protection of participant owners (informed consent, personal data, risk of identification, risk of financial loss)
  - Protection of the welfare of animal subjects under investigation
  - Does the work involve physical interventions to the animal subjects?
  - Are these physical interventions covered under the provisions of the veterinary surgeons act or is a home office license required?

Frameworks for research involving animals - RVP, CVR and ASPA

- Home Office license under ASPA

Planned work is not CVR AND involves procedures that breach the lower threshold outlined in ASPA

- RCVS - Routine veterinary practice

Investigation and management involving procedures and techniques likely to be of direct benefit to the individual animal(s)

- RCVS - Clinical veterinary research

RVP plus work concurrently has an intention to generate new knowledge that benefits animals

See FAQ

https://www.rcvs.org.uk/setting-standards/advice-and-guidance/faqs--routine-veterinary-practice-and-clinical-veterinary/

Should vets be allowed to collect blood from their patients for diagnostic purposes?

- Yes at their discretion
- Yes if there is owner consent
- Yes if there is owner consent and ethical approval
- Yes if there is owner consent and government approval
- No

Should vets be allowed to collect blood from their patients for diagnostic purposes?

Yes at their discretion
0%

Yes if there is owner consent
0%

Yes if there is owner consent and ethical approval
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Yes if there is owner consent and government approval
0%

No
0%

Should vets be allowed to collect blood from their patients for diagnostic purposes?

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Yes if there is owner consent and government approval
0%

No
0%

When a blood sample is collected from a patient for clinical reasons, should vets be allowed to collect a small amount of additional blood for research purposes?

- Yes at their discretion
- Yes if there is owner consent
- Yes if there is owner consent and ethical approval
- Yes if there is owner consent and government approval
- No

When a blood sample is collected from a patient for clinical reasons, should vets be allowed to collect a small amount of additional blood for research purposes?

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Yes at their discretion 0%

Yes if there is owner consent 0%

Yes if there is owner consent and ethical approval 0%

Yes if there is owner consent and government approval 0%

No 0%

Should vets be able to collect blood from clinical patients solely for research purposes?

- Yes at their discretion
- Yes if there is owner consent
- Yes if there is owner consent and ethical approval
- Yes if there is owner consent and government approval
- No

Should vets be able to collect blood from clinical patients solely for research purposes?

Should vets be able to collect blood from clinical patients solely for research purposes?

What is ASPA?

- The Animals in Scientific Procedures Act
- Defines:

1. Contexts and conditions for research with a possibility to cause harm to ‘protected animals’ (vertebrates and octopus vulgaris).
2. Routes to governmental assessment and approval for such work.
3. Training required for such work.
4. Institutional Conditions and protections for experimental animals.

<u>Work breaching the ‘lower threshold’ is regulated and requires a home office licence</u>

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662364/Guidance_on_the_Operation_of_ASPA.pdf

The lower threshold

A procedure is regulated if it is carried out on a protected animal for a scientific or educational purpose and may cause that animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by inserting a hypodermic needle according to good veterinary practice. This is referred to as the ‘lower threshold’.

- Is the ‘lower threshold’ too high or too low or just right?

The lower threshold

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- BUT, special provision is made for veterinary surgeons (and selected others) carrying out clinical research.

RCVS clinical veterinary research guidance

1. Advice on RVP available from advice@rcvs.org.uk
2. Ethical review is required for CVR (outside Uni RCVS offers review)

3. Informed consent is required for CVR
4. An option to withdraw without penalty (to client or animal) is mandatory and should be explicit in consent information
5. Clinical data is not covered by GDPR
   - When data use relates to animal only
   - Also need to consider privacy
6. Non-invasive procedures still require ethical approval

RCVS clinical veterinary research guidance

7. Novel procedures require a thorough harm / benefit analysis
    - Is there evidence that likely benefits outweigh likely harms?
    - Is procedure of equivalent benefit and likely to cause less harm than that currently available?
    - Will the procedure improve overall animal welfare?
    - Is there a rescue plan in place?
    - Is the context appropriate (staffing, facilities, institutional support, insurance)?
        - This is a general consideration for RVP.

8. Veterinary researchers ‘might find it helpful to consult a peer’. A record of the conversation should be kept.

Animal Treatment Certificate

- An ATC is required to carry out a clinical trial of a veterinary medicine in animals in UK.
  - Applications to VMD
- What is a veterinary medicine:
  - any substance or combination of substances presented as having properties for treating or preventing disease in animals; or
  - any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action, or to making a medical diagnosis.
  - Not food supplements and not surgical interventions

Animal Test Certificate and RCVS guidance

- Randomisation to a selection of **authorised** medicines requires an ATC and is CVR

- Randomisation to a non-authorized (RCVS uses term novel) medicine requires at least an ATC, but may or may not be CVR and may fall under ASPA

- Use of a non-authorized medicine may or may not be RVP and may fall under ASPA (i.e. implied such use may *de facto* be considered experimental)

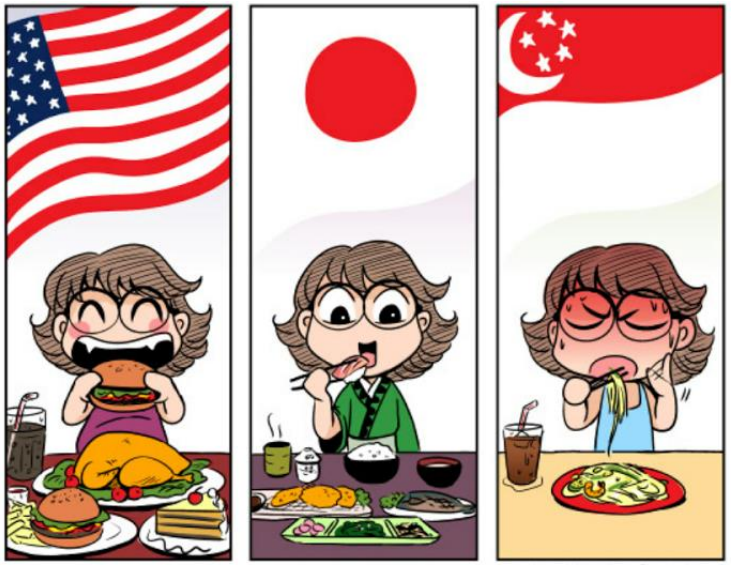
Veterinary research outwith ASPA

- Research not involving clinical interventions
  - Questionnaires
  - Superfluous tissue samples from previous clinical procedures
  - Data
  - Environmental sampling
- Research involves intervention(s) that do not breach the lower threshold
  - Pain or suffering equal to or greater than Insertion of a hypodermic needle through the skin
- Clinical veterinary research
  - Interventions are for the direct benefit of the animal or its immediate group
  - Example: doing what you would anyway and then using data for research or using surplus clinical material
  - Example: comparing two treatment approaches each of which is recognised practice
  - If uncertain we can discuss with HO inspector and RCVS RVP committee
- Recognised agricultural or animal husbandry practice
- Research covered precisely by Animal Test Certificate from VMD

Research overseas

- Important to consider that legal and cultural norms maybe different in other countries and may vary between societies within countries.

- Some examples:
  - Contact individual rather than gatekeeper
  - Research in authoritarian countries – how free is the participant
  - Can participants understand the documentation?
  - Are there legal differences in data handling



Clinical Audit

"a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change"

Publication

- Not ethical to recruit participants without intention to disseminate information
  - Huge problem in medical trials literature
- Ideally clinical trials should must registered at or before the onset of patient enrollment.
- **Similar principle for any research – reporting a negative finding may inform future researchers.**
- Selective reporting . . . distorts the body of evidence available for clinical decision-making.
- Trial results that place financial interests at risk are particularly likely to remain unpublished and hidden from public view.
- Anyone should be able to learn of any trial's existence and its important characteristics.

Integrity in research

- Vital for:
  - Ensuring data practice relies upon is as accurate as possible
  - Developing and maintaining good quality collaborative relationships
- Ethical review is beneficial, but benefit lost if we don't act in keeping with its ideals
- Duty lies with researchers, likelihood of audit is low
- Punishment for deliberate falsification can be harsh, but if falsified results lead to changes in practice they are likely to be worse for others than the researchers

After shocks of unethical research

- Anti-vaccine movement
  - MMR vaccine compliance in UK dropped from 92% to 84%
  - Cases of measles and bumps increased

https://en.wikipedia.org/wiki/MMR_vaccine_controversy

US : Anti-Vaccine Movement Causes Worst Measles Epidemic In 20 Years

http://www.forbes.com/sites/stevensalzberg/2015/02/01/anti-vaccine-movement-causes-worst-measles-epidemic-in-20-years/#366d6197ef9d

Conclusions

- Ethical standards have developed as a consequence of historical events
- Unethical intent is rare, but researchers should consider design carefully
- Communication is the ‘art of being understood’ and can be a challenge for those with a science background
- Research requires a higher level of consent than clinical work
- Animals have special protections under law, but veterinary surgeons have some leeway in regard to clinical research
- Rules on collection of personal data are very strict –familiarise yourself with GDPR if collecting any data about human participants

Further training and guidance

- The University provides online research ethics training via Epigeum
  - The link can be found on the central University ethics website
  - The ‘Research in Practice’ modules are most relevant
  - **This is mandatory for research active staff**

- The University research ethics handbook provides accessible details of typical approaches to research ethics application issues
- The RCVS ERP provides guidance documents to help veterinary professional prepare ethics applications
- Links and documents will be placed on the SVS research pages in CANVAS once ready

Thank you

- Email for queries and applications vetseth@liverpool.ac.uk

- Further information
  - UoL - Code of ethics
  - UoL - Application form, guidance notes and samples information sheet and consent form
  - RCVS/BVA report 2013
  - RCVS ASPA flow chart
  - VMD ATC guidance

Scenarios to consider

1.

- You want to determine outcomes of dogs with a particular type of cancer over the last 10 years. Some, but not all the data is in the clinical record.

- Who are your participants?
- What legal considerations are there?
- What ethical considerations are there?

Scenarios to consider

2.

- You want to evaluate a new diagnostic test. This will require use of samples from clinical patients.

- What legal considerations are there?
- What ethical considerations are there?

Scenarios to consider

3.

- You plan to map prevalence of a new infectious sheep disease as it travels across the UK.

Scenarios to consider

4.

- You have developed a new pharmaceutical intervention you hope will improve fertility in dairy cows.

- What type of study would be needed?
- Who are the participants?
- What permissions are needed?
- What else might you need to consider?

Scenarios to consider

5.

- You want to study the potential for COVID infections & transmission in wild chimpanzees. What considerations are there ?

- Human considerations
- What populations to be studied? permissions are needed?
- What else might you need to consider?

Scenarios to consider

6.

- You want to study ear cropping amongst dogs imported from the EU.

- What else might you need to consider?