9504 Learning Log

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# Lecture 1: Introduction to ethical practices

September 9, 2024

## Presession Tasks

**How to Argue- Philosophical Reasoning**

* Discusses the concept of reason and structure of arguments
* Focuses on deductive reasoning
* Aristotle: humans are rational beings
* Plato’s tripartite soul:
  + Rational part governs emotional (spirited) and physical (appetitive) parts
* Importance of constructing logical arguments
  + Good arguments: premises should lead to sound conclusion
* Deductive argument:
  + If premises are true, conclusion must also be true
  + Examples of valid vs. invalid deductive arguments
* Valid argument: conclusion follows logically from premises
  + Premises must also be true for argument to be sound
* Limitations of deductive reasoning:
  + Only works with known, true premises (which are rare)

How to Argue- Induction and Abduction

* **Inductive Reasoning:**
  + Based on predictability of nature.
  + Predicts future outcomes based on past experiences.
  + Example: Believing aspirin will cure a headache because it has worked before.
  + Conclusions are probable but not certain.
  + Can produce false results (patterns may have outliers).
* **Abductive Reasoning:**
  + "Inference to the best explanation."
  + Eliminates impossible options to find the most plausible explanation.
  + Example: Concluding someone dropped a class based on absence and circumstances.
  + Used by doctors, detectives, and in everyday problem-solving.
* **Nelson Goodman's Problem of Induction:**
  + Introduced "grue" to show the flaws in inductive reasoning.
  + Green objects before time *t* are grue, but after *t*, they turn blue.
  + Demonstrates potential contradictions in inductive conclusions.
* **Sherlock Holmes' Abduction:**
  + "When you eliminate the impossible, whatever remains, however improbable, must be the truth."
* **Counterarguments:**
  + Philosophical debates require reasons for opposing conclusions.
  + Arguments can be inductive or abductive.
  + Counterarguments lead to a deeper search for truth, not victory.
* **Socratic Method:**
  + Dialogue-based method used to seek truth.
  + Popularized by Socrates.
  + The goal is not to "win" but to refine beliefs.
* **Philosophical Reasoning:**
  + Inductive: Probable conclusions based on past data.
  + Abductive: Most plausible explanation given the available evidence.
  + Philosophers exchange arguments through dialogue to discover truth.

**Cognitive Biases**

* For instance, could some biases distort the truth of a premise?
  + Yes, cognitive biases like confirmation bias or anchoring bias can distort the truth of a premise.
  + Confirmation bias leads people to favor information that aligns with their beliefs, potentially ignoring conflicting data, which can warp the premise.
  + Anchoring bias causes undue emphasis on the first piece of information encountered, distorting subsequent interpretations.
* Could some biases lead one to a false conclusion based on true premises?
  + Yes, biases like *hindsight bias* or *framing effect* can lead to false conclusions even with true premises. Hindsight bias makes past events seem more predictable, while the framing effect alters conclusions based on how information is presented, rather than the actual truth of the premises.
* Which biases do you think can be common in science?
  + *Confirmation bias* – favoring data that supports hypotheses.
  + *Publication bias* – preference for publishing positive results.
  + *Anchoring bias* – relying on initial findings.
  + *Bandwagon effect* – following popular trends in research.
* Which biases do you think can be common in politics?
  + *In-group bias* – favoring one’s group over others.
  + *Authority bias* – overvaluing the opinion of leaders or experts.
  + *Negativity bias* – focusing on negative events or issues.
  + *Framing effect* – swaying public opinion through how issues are presented

**Its time to question Bio engineering**

* **Primary message** 
  + The speaker highlights the unprecedented power humans now have to intentionally design living organisms through biotechnology, raising ethical questions about how we should manage this power, especially as it relates to animals and potentially humans.
* **Main conclusion** 
  + Humans are entering a new phase of *intentional evolution* where we design organisms.
  + Ethical considerations about modifying life forms are crucial, as we are no longer just manipulating environments but organisms directly.
* **Premises** 
  + Humans have been altering evolution since civilization began, through environmental changes.
  + Biotechnology allows direct manipulation of life, a fundamental shift from past evolution.
  + Ethical concerns must accompany advancements in genetic manipulation.
* **Delivery style** 
  + uses a calm, explanatory tone, laying out scientific advancements in a logical sequence.
  + The pace is deliberate, helping the audience grasp complex ideas while emphasizing the gravity of ethical implications.
  + The use of striking examples, like bioluminescent animals and cloned organisms, makes the discussion both engaging and thought-provoking.

Are you ready for the genetic revolution

* **Primary Message:**
  + humanity is at the brink of a major transformation where we will take control of our own evolution through genetic technologies like CRISPR, raising both profound opportunities and ethical responsibilities.
  + The future will be shaped by the choices we make now in how we use these technologies in health care, reproduction, and societal structures.
* **Main Conclusions:**
  + Precision gene editing will revolutionize healthcare, moving from generalized to personalized medicine.
  + Genetic technologies will extend beyond healthcare, affecting reproduction, human traits, and even societal competition.
  + Ethical dilemmas arise as different cultures and countries will approach gene editing differently, potentially leading to conflicts or competition.
  + Society needs to balance scientific progress with moral and ethical considerations.
* **Premises:**
  + Genetic modification is becoming increasingly accessible and will soon allow for customized treatments and enhancements.
  + People generally want to improve health and eliminate diseases.
  + Different societies hold varying beliefs about what is ethically acceptable, which may lead to international tensions.
  + Technology will continue to evolve and impact future generations in ways that we cannot fully predict.
* **Delivery Style:**
* The speaker uses a forward-looking, urgent tone, discussing profound scientific advancements with a blend of optimism and caution. The pace is steady, allowing the audience to absorb complex ideas, while the word choices ("unethical," "profound," "transform") heighten the sense of responsibility and urgency.
* By using real-world examples like CRISPR and cultural differences, the speaker makes the argument more relatable and thought-provoking.

## Lecture notes

Primary building blocks

* Premise
* Reasoning

Basic types of relevant arguments

* Induction
* Abduction

Reasoning between science and society

* How well do scientific arguments reach society?
  + Several barriers due to complexity, communication, trust, public policy and media influence
* How do you argue with cognitive biases?
  + **Acknowledge Bias**: Start by recognizing that everyone, including yourself, may have cognitive biases. Acknowledging this openly can help create a more constructive dialogue.
  + **Use Clear and Simple Arguments**: Present information in a way that is easy to understand, avoiding overly complex data that can reinforce cognitive biases like the *complexity bias*.
  + **Appeal to Emotion and Values**: Since people often make decisions emotionally, framing scientific arguments in a way that aligns with their core values may help overcome biases like *confirmation bias*.
* Do valid truthful arguments always succeed?
  + Not always
  + **Misinformation**: In the digital age, misinformation can spread faster than truth. The more accessible and viral nature of false information can prevent valid arguments from gaining traction.
  + **Competing Interests**: Political, economic, or cultural interests can suppress or ignore valid arguments if they challenge powerful narratives or institutions.

What is clinical research

* Treatment research
* Prevention research
* Diagnostic research
* Screening research
* Quality of life research
* Genetic studies
* Epidemiology studies
* Observation studies
* Clinical trials – phase 1-4

The seven requirements

* Scientific value
* Scientific validity
* Fair subject selection
* Favorable risk benefit ratio
* Independent review
* Informed consent
* Respect for potential and enrolled subjects

Some questions and comments

* Value
  + Non generalizable results
* Expertise for evaluation – interdisciplinary
  + Scientific knowledge
  + Ethical knowledge
  + Statistical knowledge
  + Legal knowledge
* For clinical research protocol to be ethical, the methods must be valid and practically feasible
  + The research must have clear scientific objective
  + Be designed using accepted principles, methods, and reliable practices
  + Have sufficient power to definitively test the objective
  + Offer a plausible data analysis plan
* If there exists a consensus about what is the better treatment, there is no null hypothesis, and the research is invalid

# Lecture 2: Regulations of Animal Research Ethics

September 10, 2024

## Presession Tasks

Ethics of animal investigation

* Animal use is acceptable if it contributes to biological knowledge or benefits humans/animals.
* Researchers must explore alternatives (3Rs: Replacement, Reduction, Refinement).
* Humane treatment, minimal use of animals, and expert validation are required.
* Pain and distress must be minimized; extreme procedures need justification and safeguards.
* Non-recovery/no-pain procedures are acceptable; painful ones require humane endpoints.
* Physical restraint should be minimized.
* Painful experiments for instruction or demonstration are discouraged; alternatives should be used.

Should animals be used for scientific of commercial testing

* Animals are used for developing medical treatments, testing medication toxicity, and ensuring product safety.
* Animal research dates back to at least 500 BC.
* Ancient Greek physician-scientists (Aristotle, Herophilus, Erasistratus) practiced vivisection to study organisms.
* Vivisection was done on human criminals in Rome/Alexandria but shifted to animals in Greece due to mutilation prohibitions.
* Aristotle believed animals lacked intelligence, while Theophrastus argued against vivisection, believing animals feel pain and harming them offends the gods
* Pros
  + Animal testing contributes to life-saving cures and treatments for humans and animals alike.
  + Animals are appropriate research subjects because they are similar to human beings in many ways.
  + Animal research is highly regulated, with laws in place to protect animals from mistreatment.
* Con
  + Animal testing is cruel and inhumane
  + Animal tests do not reliably predict results in human beings.
  + Alternative testing methods now exist that can replace the need for animals.

Failure of animal experiments

* Animal experiments for medical and product testing often cause suffering to millions of animals yearly.
* Animals differ from humans in metabolism and reactions, making many tests unreliable.
* Many experiments cause artificial diseases in animals, which don't reflect human conditions.
* Success in animals does not guarantee effectiveness in humans, as over 90% of treatments fail in clinical trials.
* Painful and trivial experiments persist without sufficient justification.
* Alternative methods, like human cell cultures, offer more relevant and humane results.
* Industry profits from animal testing despite questionable benefits

Can we do science without animal testing

* Animal experiments provide data to assess food, medicine, and product safety, but they are expensive and cause suffering.
* Society and scientists increasingly oppose animal testing.
* Alternatives, such as organ-on-chip, tissue cultures, and computer models, can better mimic human biology.
* The "3 Rs" approach:
  + **Replacement**: Using cell technology or computer models instead of animals.
  + **Reduction**: Using fewer animals through better study design.
  + **Refinement**: Improving animal welfare.

Understanding the OCD brain and animal testing

* Researchers study OCD-like behaviors in rats and primates by manipulating specific brain circuits.
* Rats with inactivated frontal cortexes show increased repetitive checking behaviors, mimicking OCD symptoms.
* Marmosets are used for more complex behavior studies, as their brains are closer to humans.
* Animal studies help identify brain circuits involved in OCD, which can't be fully studied in humans.
* The goal is to develop better therapies for OCD, balancing the ethical concerns of animal research with patient suffering.

## Lecture notes

* Can manipulate mice and fish

What do you think the main purpose of animals used in research was in Canada

* Most of the animals were used in fundamental science

What did animals experience? Categories of invasiveness

* Level e is predator and prey relationship

Regulation of research involving animals

* External Regulatory Bodies Overview
* Internal Accountability Structure
* Institutional Policies & Procedures
  + Highlights - Animal Ethics and Care
  + Program at Western and Affiliates

External Regulatory bodies

Federal

* Criminal code of Canada
  + XI, Sects 445 – 447 Protection of animals from cruelty, abuse & neglect
  + It is illegal to cause unnecessary pain, suffering, or injury to an animal, and research facilities must comply with these regulations when conducting experiments involving animals.
  + The law distinguishes between legitimate scientific research and activities considered cruel or abusive, allowing for legal repercussions if the research crosses ethical boundaries.
* Tri-Agency – Sect 3.5 ‘Research Involving Animals’
  + Any research involving animals must be ethically justified. The potential benefits of the research must outweigh the potential harm to the animals involved. The use of animals must be essential to achieving the research goals
  + The guidelines emphasize the importance of proper care and handling of animals. This includes ensuring that animals have appropriate housing, nutrition, and veterinary care, and that they are monitored closely to minimize any distress or suffering.
* Wont get funding if you do not have a certificate

National

* CCAC
  + Is not the law
  + Advisory
  + Set the rules and regulations
  + CCAC is responsible for overseeing the ethical use of animals in research, teaching, and testing in Canada.
  + It ensures high standards of animal care and use to promote ethical animal treatment in research environments
  + he use of animals in research must follow the "Three Rs" principles:
    - **Replacement**: Use alternatives to animals when possible.
    - **Reduction**: Use the minimum number of animals needed for valid results.
    - **Refinement**: Improve animal welfare by minimizing pain and distress.
* Canadian Association of Laboratory Animal Medicine (CALAM)
  + CALAM Standards of Veterinary Care (2007)

Provincial

* Ontario Ministry of Agriculture Food and Rural Affairs (OMAFRA)
  + Animals for Research Act
* They are important
* Cant say no, they will shut you down

Internal accountability structure

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Tier 1: Senior Administrator Responsible for Animal Ethics and Care Program (AECP) - Vice President – Research

* Maintain CCAC GAP Certificate
* Equip an Animal Care Committee
* Appropriate Animal Care Facilities & Operations
* Adequate Veterinary & Animal Care Staffing
* Ensure Alignment with External Regulations
* Informed Animal Users Sound Pre- & Post- Approval Monitoring Structures
* OH&S Protection from Animal Hazards
* Active Engagement in CCAC Assessments
* Ultimate responsibility for the animal ethics & care program within Western’s Research Community

Tier 2: The animal care committee

* Animal Ethics reviews of Animal Use Protocols (3G – eSirus)
* Training and Post Approval Monitoring program oversight,
* e.g. Continuing Care Visits, site visits etc
* 1st tier response to ‘Concerns’
* Delegated authority by VPR for unrestricted access and to intervene to relieve unnecessary animal pain or suffering
* Development and review or all related procedures and SOPs
* Membership
  + Institutional veternian
  + Institution OHS officer
  + Category 1 – Animal-based scientists
  + Category 2 – Community representatives
  + Category 3 – Non-animal user institutional employees
  + ACC Chair
  + ACC Vice Chairs
  + Face to face regular meetings – consensus-driven decision- making
  + ACVS Director
  + ACC Coordinator
  + Category 4 – Institutional veterinary technicians
  + Category 5 – Institutional students
  + Category 6 – Animal Care facility supervisor

Tier 3 – Animal care and veterinary services

* Registered veterinary technicians (RVTs)
* Institutional veterinarians with unrestricted access to animals and authority to assess and intervene in response to sick animals
* Animal husbandry staff
* CCAC-mandated trainers
* ACC administrative leaders and staff

A diagram of a pyramid

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# Lecture 3: The 3R’s of ethics

September 15, 2024

## Presession Task

The 3 Rs

* **Replacement**:
  + Basic: Avoiding or replacing animals in experiments.
  + Updated: Developing predictive models and tools to replace animal use.
  + Full replacement: Use of human tissues, cells, and computer models.
  + Partial replacement: Use of invertebrates or animals not capable of suffering, and tissues from animals not used in painful procedures.
  + Technologies like human cell cultures, computer models, and stem cell techniques are used.
  + Partial replacement involves using species that cannot suffer, such as invertebrates.
* **Reduction**:
  + Basic: Minimizing the number of animals used.
  + Updated: Designing robust, reproducible experiments to maximize information gained per animal.
  + Examples: Longitudinal imaging, microsampling, sharing resources.
  + Techniques like better experimental design, longitudinal imaging, and data sharing maximize data from fewer animals.
* **Refinement**:
  + Basic: Minimizing pain, suffering, and harm.
  + Updated: Improving animal welfare through better housing, anaesthesia, and training animals to reduce stress.
  + Impact: Reducing suffering improves the reliability and reproducibility of results.
  + Improving housing, handling, and experimental techniques (e.g., anesthesia, environmental enrichment) to enhance welfare and experimental accuracy​

Animal Welfare

* **Stress and Animal Welfare**: Stressed animals (from fear or boredom) provide unreliable data, making refinement not just ethical but scientifically beneficial.
* **Future Optimism**: Alternatives to animal use are improving, but complete replacement of animals in research is not yet possible.
* **Reproducibility Issues**: Global concerns about reproducibility in science; reproducibility is critical for reliable scientific data, especially in animal research.
* **ARRIVE Guidelines**: 20 principles for reporting animal research, helping ensure studies are reproducible and reliable.
* **Shift in Scientific Focus**: Importance of moving from a quantity-focused approach (publishing many papers) to emphasizing the quality and reproducibility of research, particularly in animal-based studies.

## Lecture notes

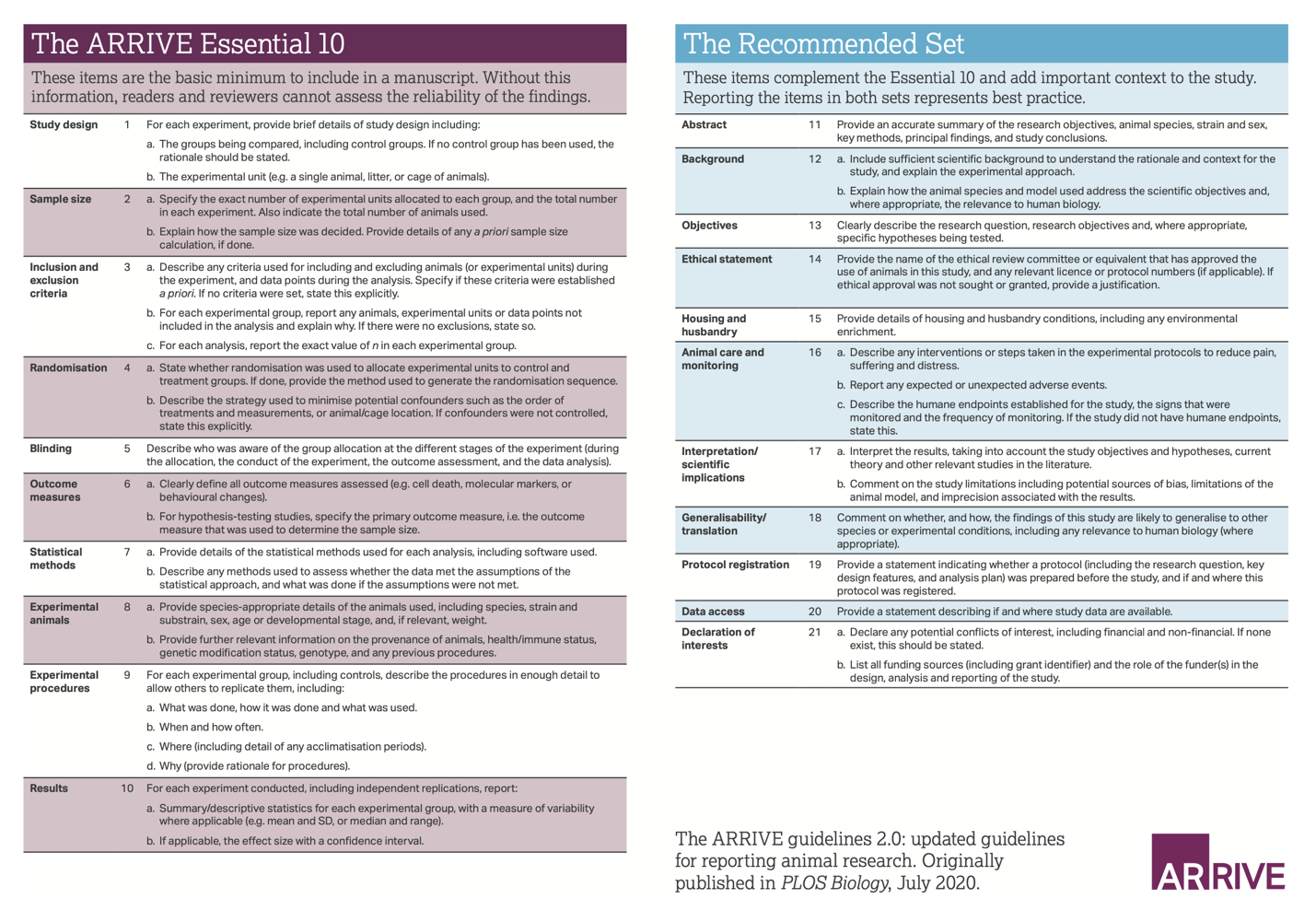
* sex wasn’t incorporated in medical experiments for animals for a while
* high effect and sats significance
* human ethics don’t question enough
  + a lab can be chasing the p value of 0.05, but might be unreplicable for other labs, so then they don’t publish
  + and then when the ethics board picks it up they are content, but don’t question it
* don’t do a good job when doing alt searches
  + protocols of level E have to do alt search’s

Replacement

* methods which avoid or replace the use of animals
* using mathematical models
* human experiments
* using computer programs
* In vitro experiments
* Using full lifeforms
* No journals have negative results
* Reproducibility 🡪 can other laps reproduce the same results
  + Wasting time, money, animals
* Same animals in their environment
* Multi Labortory studies: More is better than 1
  + National Preclinical Sepsis Platform: developing a framework for accelerating innovation in Canadian sepsis research
  + A Preclinical Consortium Approach for Assessing the Efficacy of Combined Anti-CD3 Plus IL-1 Blockade in Reversing New-Onset Autoimmune Diabetes in NOD Mice
* Things are moving in the right direction in invitro
  + Pharmacokinetic and pharmacodynamic (PK/PD) analysis required to advance drug compounds towards clinical testing is commonly carried out in animals, however, the results are often not predictive of human outcomes
  + The high failure rate of drugs in clinical trials is in part due to fundamental interspecies differences between humans and animals used in preclinical testing, which often lead to incorrect predictions of critical human PK/PD parameters (e.g., clearance, safety margins, toxicity, efficacy)

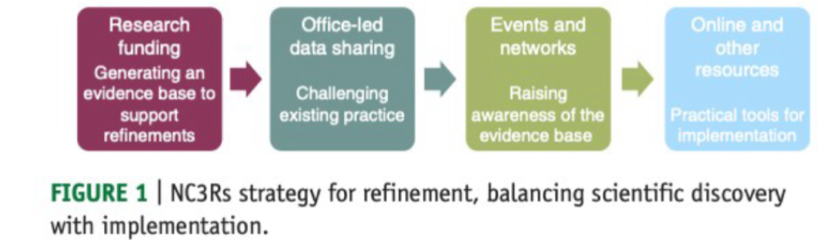
Reduction

* Methods which minimise the number of animals per experiment
* Imaging
* Sharing results
  + Publish
    - Publish all data negative or positive
  + Present
* Careful design and analysis
* No justification how you are collecting
  + Chasing power 🡪 unethical
* Prepare guidelines
  + Checklist before the checklist

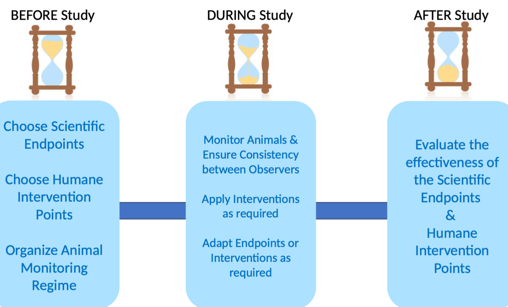


Refinement

* Methods which minimis animal suffering and improve welfare
* Imaging
* Shorter experiments
* Better housing
* Better handing
* Better pain relief
* Evidence suggests that pain and suffering can alter an animal’s behaviour, physiology and immunology variation in experimental results that impairs reliability and repeatability of studies.
* GOOD ANIMAL WELFARE IS LINKED TO THE QUALITY OF RESEARCH DATA  
  WELFARE = HOW AN ANIMAL IS COPING WITH THE CONDITIONS IN WHICH IT LIVES
* Refinement applies to all aspects of animal use ex. housing that allows the expression of species-specific behaviours, using appropriate anaesthesia and analgesia to minimise pain, training animals to cooperate with procedures to minimise any distress.
* Why is refinment important
  + preserves animal welfare
  + increases validity of animal models of human disease
  + optimizes the number of animals required to reach statistical significance
  + improves reproducibility of animal studies
* What Strategies can we use to promote Refinement & Best Welfare Practices in the scientific community?
  + funding research to generate evidence to support refinements/show that refinements are beneficial to research outcomes
    - ex. analgesic use in RA or sepsis models
  + data sharing to challenge existing practices - working/strategic groups, “white papers
    - ex. AVP position statements on Care for Chronic Implants
    - ex. CCAC standards for cage sizes



* Institutional veterinarians mainly focus on refinement of procedures... Involves consideration and optimization of:
  + HUMANE INTERVENTIONS,
  + EARLY ENDPOINTS,
  + RIGOROUS MONITORING PRACTICES
* Refinement at western
  + Refinement at the Post Approval Monitoring (PAM) level occurs prospectively, actively (when research is occurring) and retrospectively
  + Prospectively – during review of the AUP, we can prepare ourselves on outcomes and needs of the animals to alleviate any welfare concerns
    - ex. a PI wants to bring in a new species we’ve never housed before
  + Actively – typically, these active changes occur through the Animal Welfare Assessments, Sick Animal Response Program and (sometimes) through the Concerns Policy
    - ex. animal present with illness/morbidity beyond what was anticipated in the AUP
  + Retrospectively – as data is collected and analyzed and/or if the PAM program and/or PI self-reports increased morbidity/mortality
    - ex. an investigator asks for more animals on their AUP because cancer cells that were injected  
      never metastasized during the proposed timeline

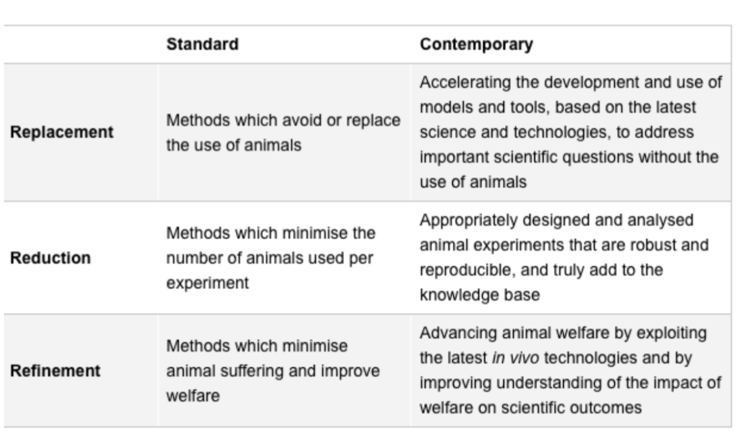


COWI assigned to protocols

* prospectively
  + continuous learning and review process to verify predictions
* retrospectively
  + used to improve the accuracy of the prospective process
* Focused on recognizing the experiences of individual animals captures how these experiences impact their welfare.
* As many categories as required will be used to describe the animals’ experiences with the protocol (as opposed to assigning all of the animals in the protocol to the highest category experienced by one individual animal.
* COWI assignment will (...in process) provide a framework for Post Approval Monitoring practices to assign oversight frequency ◊ more chances for refinement practices increased welfare!

Touch screen hit all 3Rs

* Refinement. Consistency is important to minimize variability, maximize replicability in the data produced.
* Replacement. NHPs for rodents.
* Reduction. Decreasing animal numbers, increasing per-animal data yields and facilitating the sharing of data and resources between investigators.



3 more Rs

* Repeatability (eg, same team, same experimental setup): the measurement can be obtained with stated precision by the same team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same location on multiple trials.
* Replicability (eg, different team, same experimental setup): the measurement can be obtained with stated precision by a different team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same or a different location on multiple trials.
* Reproducibility (eg, different team, different experimental setup): the measurement can be obtained with stated precision by a different team, a different measuring system, in a different location on multiple trials

# Lecture 4: Transparent and Translational Research

September 18, 2024

## Presession tasks

Improving transparency and ethical accountability in animal studies

* **Controversy around animal research**: The use of animals in research is a polarizing issue, with public and activist opposition sometimes leading to violent protests against researchers.
* **Public transparency**: Governments and scientific organizations advocate for greater transparency in animal research. Several countries, like Denmark and the UK, now publish summaries of approved animal experiments.
* **Challenges in linking ethical approval to results**: Current transparency measures do not always connect ethical approvals to published scientific results, limiting the ability to verify compliance with regulations.
* **Proposed solutions for improved transparency**:
  + Require full legal references and details about ethical approvals in journal publications.
  + Include ethical approval documents as part of supplementary materials in publications.
  + Create a comprehensive, publicly accessible database of animal studies, similar to human clinical trial registries.
* **Concerns over database creation**: While a database could increase transparency and reduce publication bias, challenges include legal, financial, and administrative burdens, as well as fears of public backlash or targeted attacks against researchers.
* **Legal and ethical issues**: Laws on freedom of information could allow public access to ethical approvals, but concerns over researcher privacy and safety persist. Measures to protect researchers from extremist threats need consideration.
* **Public impact**: Increased transparency could help build public trust and understanding of the necessity of animal research, but may not prevent opposition from extremist groups who seek a complete ban on animal experiments.

Can prospective systematic reviews of animal studies improve clinical translation?

* **Systematic reviews (SRs)**:
  + SRs are powerful tools used to improve the quality of evidence by exposing weaknesses in study design and conduct.
  + SRs have been applied to animal studies to address issues like poor quality, lack of randomization, and blinding.
* **Application of SRs in animal studies**:
  + SRs help identify gaps in research, improve study quality, and reduce unnecessary duplication of experiments.
  + Prospective SRs (conducted before clinical trials) are suggested to evaluate safety and efficacy before proceeding to human trials.
* **Challenges with prospective SRs**:
  + Despite their value, SRs may not always predict safety and efficacy in humans due to differences between animal and human biology.
  + In some cases, clinical trials have proceeded even when animal studies were inconclusive or flawed.
* **Retrospective SRs**:
  + SRs conducted after clinical trials can explain why certain treatments failed or caused harm, highlighting missed opportunities for better decision-making prior to trials.
* **Predictive limitations of animal studies**:
  + Evidence shows that animal studies do not always reliably translate to human outcomes.
  + Discordance between animal and human study results is common in fields like stroke, brain injury, and heart failure.
* **Concordance between animal and human studies**:
  + Concordance rates between animal and human studies vary widely (0-100%).
* Even with improved study design, translation from animals to humans remains unpredictable due to inherent species differences.
* **Feasibility of prospective SRs**:
  + Animal and human studies are often conducted concurrently, making prospective SRs difficult to implement in practice.
  + There is a need to reassess the role of animal studies in the development of clinical knowledge, as they are not always essential for clinical progress.

Neuroscientific Research on monkeys

* **Complexity of the human brain**:
  + Contains 85bn nerve cells and trillions of interconnections.
  + Processes information, leading to consciousness and thought.
  + Brain can only be studied while alive and functioning inside the body.
* **Challenges in studying human brains**:
  + Involves invasive techniques, often requiring skull drilling, posing risks like infection or brain damage.
  + Few volunteers willing to undergo such procedures.
* **Use of primates in neuroscience**:
  + Primates are used as models due to similarities in brain structure and function with humans.
  + Raises ethical concerns since monkeys cannot consent, and they likely suffer similarly to humans.
* **Geographical trends in primate research**:
  + In Europe and America, neuroscience research using monkeys is declining due to pressure from animal-rights groups and restrictive laws.
  + In China and Japan, such research is increasing, with significant investments.
* **Strategic concerns for the West**:
  + Allowing China to advance without comparable Western research could lead to strategic dependency.
  + China is attracting top researchers, creating new methods to study and manipulate the brain.
  + West should maintain a competitive neuroscience research program to avoid reliance on China for knowledge or treatments.
* **Ethical dilemmas**:
  + China's brain research may have military implications, including neuro-weapons.
  + Western countries might be forced to rely on ethically questionable research from China and Japan for medical treatments.
  + A call for the West to conduct its own research, adhering to its ethical standards.
* **Alternative methods**:
  + Some experiments could be replaced by computer simulations or brain cell cultures, though this isn't sufficient yet.
* Non-invasive brain scanning hardware is commonly used in human studies, but getting sensors inside the skull is still a challenge.
* **Future possibilities**:
  + Tools for brain research are becoming smaller and less invasive.
  + Injectable, connected silicon dust might one day replace larger brain implants.
  + Until then, primate research remains necessary as humans lack sufficient understanding of their own brains.

## Lecture notes

Reading 1

* Governments and scientific entities have called for increased transparency and an informed dialogue between regulators scientists and the concerned public.
* 1) a requirement in journal articles to provide the complete legal reference, including the name of the ethical entity that gave authorization and the project reference # (Oz experience?)
* 2) approval docs supplied as part of the supplementary online material.
  + Extra figures and western blots
    - Not really key but important to have them in the paper
* 3) setting up a comprehensive, prospective database of animal studies that includes details of the ethical approval, subsequently published articles and other material reporting the results of the study. – registration/pre registration
  + Should the public understand whats being researched

Reading 2

* Systematic reviews (SRs) are powerful tools with the potential to generate high quality evidence. Their application to animal studies has exposed the poor quality of the majority of these studies, highlighting that many essential procedures such as randomisation and blinding are frequently not performed or reported.
* SRs use already available data (producing new scientific information without using more animals) and can prevent the unnecessary duplication of animal experiments by establishing the status of a body of evidence in a field.
  + How do we assess the relative contributions
    - Whats the point of using animals if we are you running the animal tirals parallel to human trials
* They have potential to do so, as they can make the evidence obtained from animal studies more transparent and accessible.
* Take home message
  + While SRs of animal studies conducted prior to clinical trials would provide valuable evidence about the validity of the animal data, they  
    would not necessarily be able to reliably predict the safety or efficacy of interventions when trialled in humans, due to the poor predictivity of the primary studies.
  + Suggest that it is time to assess the relative contributions of animal and human research in order to better understand how clinical knowledge is actually produced.

Reading 3

* Ethical considerations.
* Knowledge and advancement (clinical and  
  military) sharing.
* Leaving others to do the ‘dirty’ work? ... but using the technology, if you can get it?

Traansfer of Sceintific data to next phase

* Role of human ethics board?

A diagram of a medical procedure

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A diagram of a diagram of a scientific experiment

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* Reproducibility is at the top 🡪 want to make sure to get it right over and over again
* Funding 🡪 people often cut corners
* We can reproduce 🡪 we are wasting money 🡪 wasting animals

Identifying transparency and translational gaps – irreproducible data

* Percentage of studies reported to be irreproducible
* Bad science (based on lack of transparency? or bad reporting?
* Significant drop in reproducibility

Reports

* Amgen (Begley & Ellis, 2012) and Bayer (Printz et al, 2011) were unable to replicate significant percentages of published studies
* A team at Bayer HealthCare in Germany reported that only about 25% of published preclinical studies could be validated to the point at which projects could continue.
* Over the past decade, before pursuing a particular line of research, scientists in the haematology and oncology department at the biotechnology firm Amgen in Thousand Oaks, California, tried to confirm published findings related to that work. Scientific findings were confirmed in only 6 (11%) cases
  + Wasting 90% of time and money

Transfer of scientific data to next phase

* Waste
  + Animals
  + Peoples time
* Ethical issues
* Cost
* Loss of public and policy makers confidence in science
  + Laws get made 🡪 things will come and go
* Fuel for animal rights organizations
  + Scientist’s find it hard to stand up in front of a group that have different opinions
* Role of human ethics boards
  + Look at the evidence properly

A diagram of a scientific research

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* Why aren’t they working
* `study design
* Detail analysis and reporting
* Recants is still a major problem
* Laboratory protocols are still a standard and we are all following the regulations
  + Can remove variability of environment

Questionnaire on reproducibility in research A comparison of a graph

Description automatically generated with medium confidence

* Similarities between the two graphs
  + Pressure to publish
  + Not replicated enough
    - Compromises
  + Method codes unavailable
  + Better mentoring and supervision
    - Sometimes pI are so busy that students are doing it

Transparency- data reporting – there are gaps

* Voluntary guidelines are very important, but journals need to take tangible steps to implement them with standards flexible enough to work for a broad range of  
  studies,”
* Voluntary reporting guidelines for animal studies, which have been endorsed by hundreds of research journals, are largely being ignored.
* Poor transparency (reporting?) = poor/low translation
* Should tell us whether double blind was being use
* Now its not being enforced as much

And other reasons for poor reproducibility

* Pressure to publish
  + Publish in high impact factor journals
  + Publish only positive findings
  + Very few negative data are published
* Hard-to-get grant dollars
  + Increases pressure to publish, especially positive data
  + Increases pressure to publish underpowered studies
* Pressure to confirm a hypothesis (investigator bias)
  + Failure to blind subjective observations
* This bias contributes to the pressure to publish positive results (Journal/reviewers?)
* Chance to replicate get harder as p value gets smaller
* Doing an experiment once is not good enough
* Better to chase effect size rather than p value

Definitions of Reproducibility and rigor

* Reproducibility
  + Methods reproducibility - Providing enough procedural detail and data to repeat successfully
  + Results reproducibility - Getting the same results from a new study with procedures as close to the original as possible
  + Inferential reproducibility - Drawing similar conclusions or making knowledge claims of similar strength from study replications and re-analyses
* Rigor
  + Application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation, and reporting of results.

Begley’s six rules for reproducibility

1. Were studies blinded?
   1. Do you know what the treatments were
   2. Were investigators blinded
2. Were all results shown?
3. Were experiments repeated?  
   - Technical  
   - Biological
4. Were positive and negative controls shown?
5. Were reagents validated?
6. Were the statistical tests appropriate?
7. How did they allocate the group
8. Mentioning the species in the methods and in the title
9. Sex was not appropriate documented
10. Age 🡪 studying dementia in new borne mice… doesn’t really make sense
11. Group size is really low

Robust study design tools

* Experience
  + Cant underestimate the PI experience
* AI/computers

Model selection and justification

* Evidence demonstrates that critically important physiological and genetic differences between humans and other animals can invalidate the use of animals to study human diseases, treatments, pharmaceuticals, and the like.
* Are people using the evidence

Risk benefit analysis of translation research

* Translation: Applying results from preclinical research, usually via late-stage preclinical animal studies, to justify, design and inform trials in humans.
* Using animals for scientific purposes is acceptable only when any harm done to the animals is very greatly outweighed by the benefits of their use’
* Consider
  + How much harm? What kind? To whom?
    - The 3Rs and beyond
  + How much benefit? What kind? To whom?
    - Research - value/question – fundamental vs clinical/biomedical based
    - Teaching - enhance students learning and skills?
    - Testing – implants, drugs ?
* Actions have risks, inaction (doing nothing) also has risks. What is the potential harm of choosing to do

Benefit Domains and Harm factors

* Benefit domains
  + Social benefits
    - Human health
    - Animal health
    - Environment health
  + Socioeconomic benefit
  + Scientific benefit
  + Educational benefit
  + Safety and efficacy
* Harm impact on five freedom
  + Freedom from pain/ injury
  + Freedom from fear/ distress
  + Freedom from hunger/ thirst
  + Ability to express normal behaviour
  + Freedom from discomfort/ appropriate husbandry

The outcome

* Listing the benefit and harm of the animals
* What’s the benefit and harm to society and environment
* By not doing anything this is also unethical

Current concepts of Harm–Benefit Analysis of Animal Experiments – Report from the AALAS–FELASA Working Group on Harm–Benefit Analysis

A white paper with black text

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NIH

* A diagram of a method

  Description automatically generated with medium confidencestatement on enhancing rigor, transparency and translatability in animal research
* Unfortunately its been a couple years and nothing has been to change them
* Maybe change it by mandating and more education
  + Perhaps you must do arrive guidelines to get a grant

A close-up of a paper

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Design and getting to publish negative results

A blue arrows with white text

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* Current process of how we publish data

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Reading 1: what about the public?

* Nevertheless, it is to be hoped that increased transparency would increase levels of public sympathy and understanding towards animal research, as the public would be more aware of the progress made possible through the use of animals.
* However, one has to accept also that transparency alone will not appease, nor prevent, the actions of extremists, whose goal is the complete abolition of all animal experiments.

Responsibility and the public

* Public still think we are secretive
* Poor welfare standards
* Public doesn’t think we are dishonest
* The data hasn’t changed much and work needs to be done regarding the public
* Public perceived that GMO was and issue and then mandates were made even though there are years worth of research that says otherwise
  + THIS IS WHY ITS IMPORTANT TO BE TRANSPARENT

Activity

* Cathy is warm, unsure whether she is trustworthy or honest
* Cathy is intelligent but not confident
* Would be happy to have her as neighbour
* 1-2 because I don’t know whether or not I can trust them
* 4 neutral because just because they hide the research it doesn’t mean that its not good
* 4 neutral because even though they are giving them RA there are also treating and finding vaccine for RA
* facility is not vary transparent

# Lecture 5: Moral principles of animal research

September 23, 2024

## Presession notes

**A New Framework for Animal Research Ethics**:

* **Core Values**: Two main ethical principles: *social benefit* (ends of the research) and *animal welfare* (means to achieve it).
* **Key Principles**:
  + **No Alternative Method**: Animal research should only be used when there is no other viable method.
  + **Expected Net Benefit**: The potential benefits of the research must outweigh the risks and costs.
  + **Sufficient Value to Justify Harm**: The harm caused to animals should be justified by the potential social or scientific benefit.
  + **No Unnecessary Harm**: Only harm necessary for the scientific purposes should be inflicted.
  + **Basic Needs**: Animals’ basic needs, like food, shelter, and proper care, should be met.
  + **Upper Limits to Harm**: Animals should not endure severe suffering for prolonged periods of time.
* **Decision Tree**: The decision-making process in animal research is based on whether these six principles are met.

**Case Study: Moderna COVID-19 Vaccine Research**

* **No Alternative Method**: Animal trials were essential, even though human trials had begun.
* **Expected Net Benefit**: The vaccine's potential benefits were significant enough to justify the trial.
* **Sufficient Value**: Most people would agree that the harm done to animals was justified by the public health impact of the vaccine.

**Differences from the 3Rs (Replacement, Reduction, Refinement):**

* The new framework goes beyond the 3Rs, addressing areas like *basic needs* and setting ethical *limits on harm*, which the 3Rs don't fully cover.

**Key Questions & Responses:**

* **Preserving Animal Dignity**: The framework respects moral status but balances practical considerations.
* **Reuse of Animals**: Reusing animals in multiple experiments poses ethical dilemmas, and this practice needs further ethical consideration.
* **Creating Animal Models for Disease**: The framework allows for this if all principles are met, but there’s concern about the quality and validity of some models.
* **Incentivizing Alternatives**: Financial incentives, leadership, and cultural change in institutions could promote the use of alternatives.

Get Real Podcast: The DMD Heroes of Texas A&M

• PETA's main target in these studies

• dogs carry genes for duchene muscular dystrophy

• often dogs are used in these studies

• speaker is a lab animal veterinarian

• producing the best research

◦ getting good results

◦ least harm to animals

• veterinarians need to have large amounts of knowledge

◦ welfare of animals

Duchene Muscular Dystrophy studies

• she worked directly with the dogs and the researchers

• who is involved

◦ veterinary technicians

◦ care staff

◦ lab animal veterinarians

• dogs get checked everyday

◦ get specialized kibble

◦ weighed once a month

• affected animals

◦ thickened tongues

◦ crunching kibble is harder

◦ they get normal kibble, that is watered down to get a consistency they can consume

◦ specific instructions for each animal

◦ have lots of special needs

◦ with the research facility for a long time

‣ up to 10 years

‣ have the option to euthanize them when they can no longer walk

• all the dogs

◦ pair housed

◦ designed so they can interact with other dogs, but they don't have to

◦ they have play groups during the day

◦ toys, they get novel items

◦ scent and texture are also used to enrich the dogs

◦ treats; not limited

◦ special treats for affected animals

• progression and severity of disease in dogs

◦ overly thin dogs

‣ but they are an appropriate body condition score

‣ muscles decrease due to disease and age

◦ dogs have naturally occurring gene mutation

‣ golden retrievers have the same gene mutation as humans with duchenes

‣ researchers do bread for it

◦ dogs have weaker suckle reflex at birth

‣ but may take some time to develop

‣ around 6 weeks you can tell which ones are affected

• a little bit slower than the other puppies

‣ around 3 months

• they mimics a child around age 5 (when kids get diagnosed)

‣ 6 months of age

• mimics a 10 year old child

• at 1 year their disease stops progressing

• endpoint criteria for euthanizing

◦ when the end of the study is

◦ when they can't eat, walk, drink

◦ staff get together and have a party with the dogs

‣ care staff gets plenty of closure and time with the animals

‣ done in the same manner as pets are euthanized

• how PETA describes the testing

◦ "crude technique that could resemble medieval times"

◦ the article is misleading about what dogs are actually experiencing

‣ mimic the 6 minute walk test that children go through

‣ gait analysis; also similar to children

‣ walk on a pad to analyze gait

◦ muscle samples are taken

‣ also happens for children

‣ dogs are anesthetized; minor surgery

◦ measure muscle strength

‣ anesthetized

• so that we can control when the dogs push the step and walk

‣ see how strong foot push is

‣ little microtears happen for muscles to get bigger

• no different than a walk

‣ no different than what kids do

• lives of children with muscular dystrophy

◦ 1/3 of their life has been extended bc of animal research

◦ studies with dogs have made a difference

## Lecture notes

* Values
  + What an individual believes to be good or have worth
* Morals
  + Ideas driven by a desire to do good often for a group or community
  + Habits or behaviors with respect to what an individual believes is right or wrong
* Ethics
  + Guidelines for conduct that address questions of morality
  + Rules of conduct or society norms with respect to a group or culture

Why now

* growing public concerns about animal welfare
* growth of animal ethics as a discipline
* animals’ basic needs are more complex than initially thought (sentience = capacity to have pleasant or unpleasant experiences)
* regulations and guidelines have expanded in almost every country
* reproducibility & translation concerns
* major advances in alternatives to animals

Does the ACC do this adequality

* Most of us in the animal research community face internal ethical conflict almost every day
* Harm vs. benefit analysis needs a more robust framework - justification and benefit are often accepted with little or no modification by the ACC
* The ACC should observe proposed procedures before they approve them
* Recall the min ACC exercise and scenario
  + Is it scientifically necessary and ethically justifiable to locate the preys food in such proximity to the predator
  + What method was used to determine scientific work
  + What ethical framework was used to determine moral merit

The six principles

* Beauchamp and DeGrazia (BD) have provided a step forward in augmenting the 3Rs REGULATORY principles using the following ETHICAL framework;

A diagram of a core values

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* Framework meets three demands:  
  1. be ethically defensible - can withstand scrutiny from a diverse range of parties  
  2. be politically reasonable/responsive - a realistic chance of acceptance by these parties  
  3. be practically instructive/useful - for those engaged in review or conduct of animal research

Ethical research practice

* Ethical animal practice?
* The 3Rs are not enough because
* does not feature:  
  1. deprivation of a lab animal’s basic needs as an important type of harm  
  2. limitations on the amount of permissible harm  
  3. consideration of which scientific objectives are worth pursuing by addressing the costs or risks to human beings & anticipated harms to animals

What is the goal

* unfortunately, the ethics of animal research is often viewed through one of two opposing perspectives
* by setting current regulations in an ethical framework, it exposes regulatory strengths and weaknesses
* BD’s hope is that this framework is capable of promoting agreement between the biomedical and animal protection communities
* How? by finding points of convergence that the more open-minded individuals of each group can agree upon

A diagram of values and values

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* Open minided people 🡺 there is overlap between the researchers and animal rights activities

3 points of convergence

* 1. sentient animals have moral status. They are not merely tools of research – “animal use is a privilege, not a right”
* 2. any justification for harming (non-consenting) animals with moral status must appeal to substantial and otherwise unattainable social benefits
* 3. any permissible harming of animals in research is limited by considerations of welfare

Social benefit

* 1. No Alternative Method
  + animals must be the sole ethically acceptable way to address a research problem whose solution offers the prospect of a social benefit.
* 2. Expected Net Benefit
  + the prospect of social benefit from a research study must outweigh its expected costs and risks to human beings that exist from poor-quality or inapplicable animal data
* 3. Sufficient Value to Justify Harm
  + the prospect of a net benefit for human society from a research study must be sufficiently valuable to justify expected harms to animal subjects

Animal welfare

* 1. No Unnecessary
  + Harm animal subjects must not be harmed unless a particular harm is necessary for and morally justified by scientific purposes
* 2. Basic Needs
  + animal subjects’ basic needs must be met in the conduce of studies unless failure to meet specific basic needs is necessary for and morally justified by scientific purposes
* 3. Upper Limits to Harm animal subjects must not be caused to endure severe suffering for a lengthy period of time (unless necessary for and morally justified by critically important social and scientific purposes)

BD’s Decision tree

A diagram of a question

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* Cant have death as an endpoint

Advantages of a robust ethical framework

* growing public concerns about animal welfare
* growth of animal ethics as a discipline
* animals’ basic needs are more complex than initially thought (sentience = capacity to have pleasant or unpleasant experiences)
* regulations and guidelines have expanded in almost every country
* reproducibility & translation concerns
* major advances in alternatives to animal
* Common ground in core values = constructive communication
* Social benefit = more successful translation
* Animal Welfare = decent lives for animal subjects
* public trust & transparency
* policy change

Ethical review is a catch 22 ?

* A study could be scientifically justified but not morally justified..
* the better the model, the more justifiable the experiment becomes according to the principles of social benefit, but by the same token, the greater the potential negative impact on animal welfare, the less justifiable the experiment becomes according to the principles of animal welfare
* What use is ethics if we can’t reach a resolution?

Case example: the oncopig

* transgenic porcine model —the Oncopig Cancer Model (OCM)—is a next- generation large animal platform for the study of hematologic and solid  
  tumor oncology. recapitulates human cancer through development of site and cell specific tumors following Cre recombinase induced expression of heterozygous KRASG12D and TP53R167H transgenes
* Successful in vitro transformation and in vivo tumor formation has already been demonstrated in the OCM for three cancer types - Soft  
  Tissue Sarcomas, Pancreatic Cancer, Hepatocellular Carcinoma
* Many more possibilities exist...
* Answers Unmet Needs
* Early detection methods, Immunotherapy, Therapy development, Prognostic Indicators, Imaging modalities, Device Testing and Surgical Practice, Development of Standards/Data Sharing
* Is it ethical?

Animal research ethics

* ethical thinking should reasonably inform best practices that can be immediately implemented within the existing regulatory framework
* ethical principles indicate how socially beneficial involvement of animals in research can be made compatible with their having decent lives
* proactive & collaborative approach which engages all stakeholders interested in animal research

# Class 6: Practicalities of REB

September 25, 2024

## Presession notes

TCPS Chapter 3

Ethical Requirements for Consent

* Consent defined as "free, informed and ongoing".
* Key principles: voluntariness and respect for persons.

Voluntariness and Autonomy

* Participants must understand research purpose, risks, and benefits.
* Consent process emphasizes voluntary participation and respect for persons.
* Research without consent is prohibited.

Capacity and Third Party Consent

* Individuals lacking capacity can participate via third party consent.
* Third parties must have legal authority and consider welfare and justice.

Alternate Consent Processes

* Special consent processes for specific research types.
* Alterations to consent must meet ethics board criteria.
* Principal investigator ensures proper consent process adherence.

Informed Consent

* Full disclosure of research information is necessary.
* Participants can withdraw consent anytime without penalty.
* Incentives must not compromise voluntariness.

Ongoing Consent Process

* Consent must be maintained throughout the project.
* Researchers must inform participants of any significant changes.

Incidental Findings

* Researchers must disclose material incidental findings.
* Plans for managing such findings need ethics board approval.

Exceptions to Consent

* Emergency situations may allow research without consent.
* Specific conditions must be met, and ethics board approval required.

Debriefing and Withdrawal

* Debriefing required where consent alterations were used.
* Participants can withdraw data after debriefing, where practicable.

Decision-Making Capacity

* Variable according to research complexity and participant condition.
* Special procedures for those lacking capacity to ensure fair treatment.

Documentation of Consent

* Can be in written form or documented by other appropriate means.
* Alternative consent forms (oral, actions) used based on the context.

Belmont Report

* Purpose:
  + Establish ethical guidelines for research involving human subjects.
  + Commissioned by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
* Historical Context:
  + Initiated after public outcry over unethical research practices, such as the Tuskegee Syphilis Study.
* Key Principles:
  + Respect for Persons: Treat individuals as autonomous agents; special protection for those with diminished autonomy.
  + Beneficence: Obligation to prevent harm, maximize possible benefits, and minimize potential harm.
  + Justice: Fair distribution of research benefits and burdens; protect vulnerable populations.
* Applications:
  + Informed Consent: Information must be comprehensive, comprehensible, and voluntary.
  + Assessment of Risks and Benefits: Risks must be justified by the anticipated benefits.
  + Selection of Subjects: Fair and equitable, avoiding vulnerable populations unless directly related to research.
* Guidelines Implementation:
  + Applied through Institutional Review Boards (IRBs) for ethical oversight.
* Document Impact:
  + Influential in shaping U.S. and global ethical standards in human subject research.
  + Basis for U.S. federal regulations protecting human research subjects.

Rethinking Belmont Report

* Belmont Report published in 1979, foundational for ethical guidelines in human research.
* Calls for reassessment nearly four decades later due to evolving research landscape.
* Vague Boundary between Research and Practice: Difficulty distinguishing, as both now involve elements previously restricted to the other.
* Community Harms Not Addressed: Belmont principles focus on individual autonomy but overlook collective community harms.
* Transparency and Commodification: Increasing complexity in research raises concerns about conflicts of interest and the need for transparency.
* Protection of Vulnerable Populations: Critiques of how protectionism might exclude or overlook the needs and contributions of certain groups.
* Applicability of Ethical Principles: Questions about the direct application of principles to modern research ethics and governance.
* Update Definitions and Oversight: Proposes more inclusive and pragmatic definitions for research and practice to guide oversight more effectively.
* Recognize Community Harms: Suggest integrating a new principle or extending existing ones to acknowledge and mitigate community-level harms.
* Enhance Transparency: Emphasizes improving transparency in research protocols and practices, especially regarding conflict of interest.
* Balanced Protection and Inclusion: Calls for a reevaluation of protectionism to foster greater inclusion and participation of diverse groups in research.
* Broad Application of Ethical Principles: Recommends applying ethical principles across all stages of research to reflect contemporary ethical challenges.
* Argues that the Belmont Report, while groundbreaking at its time, may not adequately address the complexities and nuances of current research practices.
* Advocates for a thorough update or overhaul to better align with today’s ethical challenges in human subjects research.

Declaration of Helsinki

Preamble:

* Purpose: Outlines ethical principles for medical research involving human subjects, including research on identifiable human material and data.
* Intended Audience: Primarily addressed to physicians but applicable to all involved in human subject research.

General Principles:

* Physician’s Responsibility: Prioritize patient health, promote well-being, and safeguard rights in medical research.
* Medical Progress: Dependent on research including human subjects.
* Research Goals: Understand disease, enhance interventions, and ensure continuous evaluation of treatments.
* Ethical Standards: Uphold human dignity, rights, and health in research.
* Research and Patient Care: Balance between generating knowledge and prioritizing patient interests.

Risks, Burdens, and Benefits:

* Risk Assessment: Must weigh research goals against potential risks and burdens to subjects.
* Risk Management: Continuous monitoring and documentation of risks.

Vulnerable Groups and Individuals:

* Special Protections: Required for vulnerable groups to prevent exploitation.
* Justifiable Research: Only if it addresses the health needs of vulnerable groups and cannot be conducted with non-vulnerable groups.

Scientific Requirements and Research Protocols:

* Scientific Integrity: Research must be based on solid scientific principles and thorough literature review.
* Protocol Essentials: Must include ethical considerations, funding sources, potential conflicts of interest, and treatment provisions for subjects.

Research Ethics Committees:

* Protocol Review: Must be approved before starting, ensuring independence and adherence to both national and international norms.

Privacy and Confidentiality:

* Data Protection: Strict measures to maintain privacy and confidentiality of research subjects.

Informed Consent:

* Voluntary Participation: Must be informed and voluntary, with detailed disclosure of research aims, risks, and benefits.
* Special Situations: Extra caution required for dependent individuals or those who might consent under duress.

Use of Placebo:

* Conditional Use: Justifiable when no proven intervention exists or for valid methodological reasons.
* Risk Management: Must not expose subjects to substantial harm.

Post-Trial Provisions:

* Post-Trial Access: Arrangements should be made for participants to access beneficial interventions post-trial.

Research Registration and Publication:

* Transparency: Mandatory registration in a public database and ethical obligation to publish results, regardless of the outcome.

Unproven Interventions in Clinical Practice:

* Use of Unproven Interventions: Permissible under strict conditions to offer potential benefits to patients when standard treatments fail

## Lecture notes

What does it mean to be an ethicist?

Clinical Ethics

* When thinking about research ethics we think about what a good research question is
  + Specific
  + Gap in knowledge
  + At value
  + Reasonable attained value
* Ethics is a branch of philosophy concerned with the nature of good and differentiating right from wrong. It involves critical thinking about how we live and act, analyzing how our values inform our behaviors, and giving reasons for why some choices are better than others.
* In healthcare decisions made everyday may be considered 'ethical' in that they cannot be answered without appealing to values. For this reason, London Health Sciences Centre (LHSC) has a strong ethics program.
* Clinical ethics is about making value-based decisions in the delivery of health care.
* Patients, families, staff, clinicians, and trainees make ethical decisions every day. Most times, they do not need help with these decisions.
* However when difficult ethical situations arise and it is not clear what the "right" decision is, clinical ethics provides a platform to discuss the problem. The primary ethical questions that clinical ethics deals with are:

Clarifying morality and ethics

* Ethics
  + Situating our thoughts
  + Appealing to principles
  + Rational
  + Deliberative
  + Well structures
  + Intellectual framework for decision making
* Morals
  + Person
  + Intuitive
  + Difficult to argue or debate

What does an ethics office do?

* Administrative body
* Link between research ethic board and institutions they serve
* Delicate line between regulatory ethics, everyday ethics, and scientific ethics

Office of human research ethics

* The Office of Human Research Ethics (OHRE) facilitates the Research Ethics Board (REB) manage the approval and monitoring process for research involving human participants.
* All research involving humans conducted by faculty, staff or students at Western University or its affiliated hospitals or research centres/institutes must be reviewed by the REB in accordance with external ethical standards:
  + Federal (e.g., TCPS2, ICH GCP, HC, FDA)
  + Provincial (e.g., PHIPA, FIPPA, PIPEDA)
  + Local institutional requirements (e.g., UWOFA, MAPPs, Lawson/hospital policies).

Arm’s length

* REB to institution
  + Contracts, agreements, budgets, clinical impact, radiation and electric safety, technology, RCR and compliance
  + Chair accountability – faculty and un-affiliated  
    VS
  + Ethics oversight
  + Quorum

Research refresher

* What is the definition of research
  + An undertaking intended to extend knowledge through a disciplined inquiry and/or systematic investigation
* What is the purpose of research?
  + To answer an unknown research question.

Tips for ethics application success

* Consider intuitional requirements
  + In addition to ethical requirements, there are institutional requirements about data retention, confidentiality and privacy, participant approach, etc.
  + Please consider these in your study design.
  + Characterizing you data
    - Personal Information vs. Personally Identifiable Information (PII) vs. Personal Health Information (PHI)
    - Directly Identifying Information
    - Indirectly Identifying Information
    - Coded Information
    - Anonymized Information
    - Anonymous Information
    - Anonymity vs. Confidentiality and De-identify vs. De-anonymize
    - In what format is your data?
    - What is the source data?
    - In what form will the data be analyzed?
* Response documents are important
  + Response documents need to include the question/recommendation posed and the text of your response in a clear and itemized fashion.
  + Simply stating “done” or “complete” is insufficient.
  + Important to create a dialogue
  + It’s a start of a conversation
* Allow adequate time for review and responses
  + Submissions almost always require recommendations; plan ahead long before you want to start your study.
    - Determine the most appropriate board (HSREB or NMREB).
    - If submitting for Full Board review, check the submission deadlines.
    - If you know of specific time restrictions ahead of time, alert the  
      REB and start early.
  + On avg is 3 months
* Ensure completeness
  + Sufficient detail regarding study procedures is required for the application to be reviewed.
  + Incomplete submissions will be return un-reviewed.
  + Please submit ALL study documents and instruments for review.
    - E.g., data collection tools, interview guides, LOI/C, recruitment materials, etc.
    - Note: These documents must be in their final form (i.e., no  
      comments, tracked changes, etc.) to be approved.
  + No detail is too small to invlyde
* Make use of templates and guidance documents
  + Available on our website and under WREM “Help” tab.
  + These documents explain local policies and provide examples of how to formulate key documents (e.g., Letters of Information and Consent documents, recruitment materials, etc.)
  + Note: The majority of recommendations pertaining to LOI/C are  
    due to missing required details and statements for participants to  
    provide informed consent. Following the relevant LOI/C Guidance  
    Document is the best chance for minimizing recommendations.
* Develop a protocol
  + For clarity and consistency, prior to starting your WREM submission, write a stand-alone protocol and think about how you will operationalize your study.
  + Remember that logistical issues exist even in minimal risk studies.
  + The REB needs to understand the ‘who, what, where, when, and how’. This should be thought through and documented prior to submitting the WREM application.
  + Check key terms – anonymous vs. de-identified, conflict of  
    interest/commercialization.
  + Ensure accurate translation of protocol to WREM.
* Read the questions and follow the instructions
  + Full study details are important for the REB to understand what participants will experience, and to assess risks and benefits.
  + Ensure questions are answered sequentially and accurately (‘smart’ forms).
  + Read all help texts.
  + Tip: Just because a study is low risk, doesn’t mean the application  
    can lack detail.
* Consistency is key
  + It is impossible to discern the study activities if contradictory information is provided between questions or documents.
  + Good = all information clear and consistent
  + Bad = some inconsistencies, but minimal impact on ability to review; recommendations to confirm
  + Ugly = so many inconsistencies, cannot determine what the researchers are doing
  + Ensure all information is accurate.
  + When a revision is made in one part of the application, update all relevant information elsewhere.
* Think about all of your different participant groups
  + It is very common to recognize only patients or only those receiving an intervention as participants.
  + Will this study include the following populations
  + Anyone who will complete study procedures or have their data collected are considered to be a participant and needs to have their role explained in all pertinent sections of WREM.

Instructions for student evaluation:

Students should critical assess the following areas for ethical concerns

* Informed consent
  + Is there adequate protection for participants, especially those under involuntary commitments
* Voluntariness
  + Can participants in a psychiatric crisis genuinely provide voluntary consent
  + What additional safeguards should be in place
* Conflict of interest
  + How might the finial ties between the PI and AstraZeneca affect the study integrity
* Participant safety
  + Are the monitoring and safety protocols sufficient, especially for a vulnerable population
* Compensation
  + Could the stipend influence participants decision to stay in the study
  + Does it present under inducement
* Risk benefit analysis
  + Does the potential benefit of the study justify the risks, particularly in a vulnerable population like individuals with

Synthetic trachea transplantation review

* Where is the preclinical trial on animals
* What are other alternatives that can be used
* Where is the information coming from to make
  + Ex the expected outcomes
* Lack of discussion of comorbidities’
* Not much information about the development of the trachea
* What does recovery look like
* Conflict of interest
  + He is on the advisory board of the synthetic company

Cervical carcinoma

* Benefit does not outweigh the risks
* How much scientific validity does it have
* Why go against standard of care, and do no treatment
* What’s the value
  + Cumulative invasive surgery compared to one time hysterectomy
* At what point will they provide treatment fro the watchful waiting group

Nutritional proposal

* Standard of care
  + What another reasonable physician would do in the same situation
* Research is not being done for the participants but it is being done for future participants/ patients
* There is no guarantee in research
* If you are harmed by that then you are assumed by this risk
* Intervention done to extend knowledge

# Lecture 7: Informed Consent

October 1, 2024

## Presession tasks

Nuremberg code

* **Voluntary Consent Essential**: Consent must be freely given without force, fraud, deceit, duress, or coercion.
* **Legal Capacity**: Individuals must have the legal capacity to give consent.
* **Informed Consent**: Subjects must be fully informed about the nature, duration, purpose, methods, expected inconveniences, hazards, and potential health effects of the experiment.
* **Responsibility for Consent**: The duty to ascertain the quality of the consent lies with the individuals who initiate, direct, or engage in the experiment. This responsibility cannot be delegated.
* **Beneficial Outcomes**: Experiments must aim to produce fruitful results beneficial to society and unachievable by other means.
* **Design of Experiment**: Must be well-designed based on animal studies and knowledge of the disease or problem, ensuring that the anticipated benefits justify the experiment.
* **Minimize Suffering**: Experiments should avoid unnecessary physical and mental suffering and injury.
* **Risk Management**: Experiments should not be conducted if there is a high risk of death or disabling injury, except under very specific circumstances where the experimenters also serve as subjects.
* **Risk vs. Importance**: The level of risk taken should never exceed the humanitarian importance of the research problem.
* **Safety Measures**: Adequate preparations and facilities must be provided to minimize the risk of injury, disability, or death.
* **Qualifications of Conductors**: Only scientifically qualified persons should conduct experiments, and they must adhere to the highest standards of skill and care.
* **Subject's Right to Withdraw**: Subjects should be able to end their participation at any point if continuation seems impossible due to physical or mental states.
* **Duty to Terminate**: The lead scientist must be ready to halt the experiment if it appears likely to result in injury, disability, or death to subjects.

The Reality of Informed Consent

* Examine actual comprehension of informed consent (IC) among patients in clinical trials, challenging the assumption that IC leads to true understanding.
* IC is fundamental in medical ethics, meant to support autonomous patient decisions in clinical trials.
* Studies show patients often have limited understanding of IC components, questioning the ethical integrity of consent.
* Systematic review following PRISMA guidelines.
* Literature search across PubMed and Web of Science databases.
* Focus on studies measuring comprehension of IC components via questionnaires.
* Low comprehension rates across critical IC elements such as trial voluntariness, purpose, and rights to withdraw.
* Over half the patients did not understand the terms regarding placebo, randomisation, safety issues, risks, and side effects.
* Better comprehension observed in voluntary participation and right to withdraw.
* Patients' subjective impression of being informed versus objective lack of comprehension.
* Physicians’ overestimation of the quality and clarity of the information they provide.
* Consent process complexities due to varied human factors and lack of detailed understanding of research specifics.
* Significant gaps in patients' understanding of IC components, suggesting ethical shortcomings in current clinical trial practices and potentially in routine medical practice.
* Recommendations for improving IC processes to ensure genuine patient understanding and participation.
* Urgent need for enhanced methods and clearer communication to support truly informed consent in medical research and practice.

Healthcare consent act

* Purpose: Establishes rules for consent to medical treatment across all settings to enhance patient autonomy and ensure consistent application.
* Scope: Applies to treatments, admissions to care facilities, and personal assistance services.
* Definitions: Clarifies terms such as "treatment," "capacity," "health practitioner," and various types of care facilities.
* General Rule: No treatment without consent.
* Informed Consent: Must be informed, voluntary, and not obtained through misrepresentation.
* Elements of Consent: Includes the nature of the treatment, expected benefits, material risks, side effects, alternative actions, and consequences of non-treatment.
* Assessment of Capacity: Determined if a person can understand the information relevant to making a decision and appreciate the consequences.
* Presumption of Capacity: Every individual is presumed capable unless proven otherwise.
* Substitute Decision-Makers: Defines who can decide on behalf of an incapable person, including guardians, family members, and court-appointed representatives.
* Emergency Decisions: Allows for treatment without consent in emergencies where delay would worsen suffering or risk serious harm.
* Protection from Liability: Protects health practitioners acting under valid consent or in emergencies.
* Applications to Board: Provides mechanisms for reviewing decisions about capacity and treatment, including appointing representatives or contesting capacity assessments.
* Recent Changes: Updates on modifications to consent processes, definitions, and the roles of substitute decision-makers.
* Legislative History: Lists amendments to the act, enhancing or changing the rules regarding consent, capacity assessments, and treatment provisions.

Elements of successful informed consent

* Enhance protection for research subjects, especially vulnerable populations.
* Ensure proper conduct of the informed consent process in research.
* Supplemented by NIH-specific requirements.
* Not just a form but an ongoing conversation from initial contact.
* Informed consent document to be obtained from the Clinical Center website to avoid using expired versions.
* Emphasize NIH’s primary mission as research, distinct from standard medical care.
* Prospective subjects should understand potential lack of direct medical benefit and familiarize themselves with the study details before the first visit.
* Use a style that is comfortable and informative.
* Avoid reading the consent form verbatim to prevent overwhelming the subject.
* Create a relaxed atmosphere conducive to discussion and questions.
* Conduct discussions in a private, comfortable, well-lit space.
* Limit the number of staff present to ensure confidentiality and comfort.
* Discouraged to consent a subject to more than one study in a single session to avoid confusion and ensure understanding.
* Use simple language consistent with an eighth-grade education level.
* Be mindful of subjects who may not be literate or have reached the required reading level.
* For studies involving greater risks or vulnerable populations, an independent consent monitor may be present.
* An example of a consent meeting is shown where the investigator discusses the study in a conversational manner.
* Important points such as voluntariness, no guaranteed benefits, and the right to withdraw at any time are emphasized.
* The consent form should be signed in the presence of a witness.
* Participants should receive a copy of the signed consent document.
* Aims to improve the quality of the informed consent process and ensure compliance with ethical and legal standards.

Informed consent information sheet guidance

* Assist IRBs, clinical investigators, and sponsors with FDA's informed consent regulations.
* Update to include changes from the 2018 Common Rule and other federal departments/agencies' requirements.
* More than obtaining a signature; involves ongoing information exchange and comprehension.
* Ensures voluntary participation with adequate information about the clinical investigation.
* Legally effective informed consent must be obtained, except in specific emergency or special circumstances.
* Consent must be free from coercion, in a language understandable to participants, without waiving legal rights.
* Detailed explanation of the clinical investigation, potential risks and benefits, alternative treatments, and confidentiality aspects.
* Information on compensation and medical treatment in case of injury, contact details for questions or emergencies, and the voluntary nature of participation.
* Address unforeseeable risks, potential additional costs, the consequences of a participant's decision to withdraw, and other relevant aspects as needed.
* Required written documentation, with details on acceptable consent forms and methods, including electronic consent options.
* Clear delineation of roles and responsibilities of IRBs, clinical investigators, sponsors, and FDA in ensuring compliant informed consent processes.

Patients as research partners; how to value their perceptions, contribution and labor?

* Discusses the shift in health research towards including patients as active participants, termed Patient Engagement in Research (PER).
* Focuses on utilizing experiential knowledge of patients, or "patient partners," to enhance research outcomes.
* Includes public involvement in scientific research beyond traditional academic or clinical settings, promoting democratization of science.
* Recognizes the unique insights from patients living with diseases, which can guide research priorities, methods, and ethical considerations.
* Advocates for acknowledging the contributions of patient partners beyond mere participation, suggesting avenues for compensations and recognition.
* Addresses the issue where patient involvement is minimal or symbolic, advocating for genuine engagement and empowerment of patient partners.
* Discusses various forms of recognizing patient contributions: scientific, financial, personal, and altruistic benefits from research applications.
* Emphasizes the ethical need to recognize both the contributions and labor of patient partners in research.
* Suggests institutional requirements for recognizing patient contributions to foster ethical practices in research involving patient partners.
* Provides a historical perspective on patient involvement in research, showing the evolution from passive subjects to active contributors.
* Proposes specific recommendations for healthcare institutions to formally acknowledge and compensate patient partners.
* Encourages continuous dialogue with patient partners to refine recognition systems and align them with the values of the participants.

## Lecture notes

* A few (broad) theories of ethics
* Consequentialism 🡪 Can we justify lying to a person if the lie produces more good than bad? What if it is highly likely that the benefits outweigh the risks?
* Deontology 🡪 Do we always have a duty to tell the truth? Could such a duty be overridden? When? How would this be reasoned?
* Virtue 🡪 Is telling the truth a demonstration of respectable character? Is honesty the highest value to uphold? If you are not entirely transparent does this demonstrate a lack of character?
* Café study
* Informed Consent:
* One of the central ethical issues was whether Markingson was capable of giving informed consent to participate in the study. His mother repeatedly voiced concerns that he was not competent to consent due to his mental illness and requested his withdrawal from the study, but her requests were ignored.
* Questions were raised about the pressure Markingson may have felt to comply with doctors who held authority over his treatment and participation in the study.
* Conflict of Interest:
* There were concerns that the university researchers and medical professionals overseeing the study had financial ties to AstraZeneca, the pharmaceutical company funding the trial. This conflict of interest potentially compromised their ability to prioritize patient safety over research outcomes.
* Patient Safety and Monitoring:
* During the study, Markingson’s mental health deteriorated, but despite his worsening condition and his mother’s pleas for intervention, the medical team did not remove him from the trial. Eventually, Markingson took his own life while still enrolled in the study, raising questions about whether appropriate safety measures and monitoring were in place.
* Regulatory Oversight and Accountability:
* The case also highlighted failures in oversight from both the university’s Institutional Review Board (IRB) and state regulators. Critics argue that the IRB did not adequately protect Markingson or investigate concerns raised during the trial.

# Lecture 8: Case Studies

October 3, 2024

## Presession task

Elephant man drug trial

A close-up of a list of medical procedures

Description automatically generated

## Lecture Notes

* TGN1412 is a CD28 superagonist antibody, designed to activate regulatory T cells without the need for additional signals from the T-cell receptor.
* The antibody was initially considered promising for treating autoimmune diseases and B-cell lymphoma due to its ability to activate regulatory T cells.
* **Preclinical Trials and Development**:
  + Extensive preclinical testing was conducted on TGN1412 using human and non-human primate models, which showed it to be safe and effective.
  + The tests revealed that TGN1412 could expand T cells without causing inflammatory reactions in these animal models.
* **First-In-Human Trial Disaster**:
  + In 2006, a phase 1 clinical trial was conducted with six healthy human volunteers, who were given a dose much smaller than what was found safe in animals.
  + All six volunteers experienced life-threatening conditions, including multiorgan failure due to a cytokine storm, shortly after receiving the drug.
* **Aftermath and Investigations**:
  + The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK investigated the trial. While no flaws in the manufacturing or trial procedures were found, the biological effects of TGN1412 were unexpected.
  + The incident highlighted several critical issues, including inadequate preclinical testing in human cells and insufficient preparation for adverse events like the cytokine storm.
* **Lessons Learned**:
  + The trial highlighted the risks of crossing the species barrier between animal models and humans.
  + The importance of conducting thorough in-vitro studies with human cells before moving to clinical trials was underscored.
  + The need for extra caution when dealing with drugs with novel mechanisms of action was emphasized.
* **Comparison with Fialuridine**:
  + The document briefly reviews the case of Fialuridine, another drug that caused severe adverse reactions (hepatic toxicity and lactic acidosis) in a phase 2 clinical trial, resulting in the death of five volunteers. Preclinical animal models failed to predict these toxic effects in humans.
  + This comparison underscores the challenge of predicting drug safety based on animal models alone.
* **Conclusion**:
  + Drugs that appear safe in preclinical animal models may behave differently in humans. The need for better preclinical models that accurately predict human responses was emphasized.
  + It was recommended that first-in-human trials involve smaller numbers of volunteers and that potential risks be more carefully managed.

Animal ethical recommendation

**Ethical principal**: Autonomy/informed consent

* **Using organoid system- cells on a chip**
  + **there should be screening of all preclinical drugs, prior to in vivo modelling to insure immune responses are not great enough to adversely effect studying in humans** 
    - **They didn’t know about the risks**
    - **Participant says “ I don't really remember the risks being spoken about; we were given a ten page information document which we didn’t really have time to read”- Rob a participant**
    - **Had know idea of the adverse reaction**

**Ethical principal:** Virtue -Regular transparency of research data

* + There was a lack of independent/informed review.
    - Lead to adequate assessment of patient safety before trail is ever conducted
  + **Public registry**
  + **Preclinical research practice**
  + **Registry of all preclinical data in order to public (preregister drug trial with the exact protocol so the invitro and in vivo study that will be conducted**

**Ethical principal:** Beneficence (the time span that they administered the drug was not in the best interest of the participants)

* + Changes in the calculations of the starting point for drug dosing;
  + Careful consideration of the route and rate of administration – i.e. drugs should be administered by slow infusion rather than as an injection

**Ethical principal:** Maleficence

* Sequential clinical testing – one person at a time – rather than simultaneous, with an appropriate period of monitoring for sudden ill effects;
* Risk to participants bc they were healthy, high outweighed the risk bc the risk was unknown
  + Not a new idea, just a modification, Here channels
  + Early discussion between regulators and sponsors with much more scrutiny applied to novel agents and access to independent, specialist opinion;

# Assignment Feedback

## What makes preclinical research ethical

* **I see that in the first paragraph that I did not use citations correctly and overall could have refined it a bit more**
* While I focused on social or scientific value as outlined in the paper, I agree there are other areas where research can be deemed valuable, such as economic impact or educational advancements. I will consider including these broader perspectives in future discussions.
* **What kind of advantage are you discussing and is this regarding the animals, researchers, funding agencies or all of them?**
  + I appreciate the question. The advantage I was referring to primarily concerned minimizing risk to human participants, but I can see how it could also apply to researchers and funding agencies in ensuring a more ethical and well-supported study. Clarifying this would add more depth to the point.
* **Are animals not considered when thinking about risk? Would it be okay for animals to face unnecessary risk as long as humans do not have it?**
  + My intention was not to suggest that animals are disregarded in the risk assessment. The emphasis was on protecting human participants, but of course, the ethical treatment of animals is also paramount. I should have better emphasized that unnecessary risk to animals is never acceptable.
* **Could have pointed to more specific professions & included an expert to determine social/scientific value as well.**
  + Mentioning specific professions would have strengthened the argument. Including roles like clinical researchers, bioethicists, or veterinary scientists would have illustrated a more comprehensive view of those involved in determining value.
* **How might one quantify "significant enough?"**
  + I see how this could be vague. Quantifying "significant enough" could involve criteria like the potential for clinical application or measurable improvements in health outcomes. I will be more specific in future assignments when discussing thresholds for ethical justification.

## Animal investigation blog

* **This is a very generalized introduction – could be a little more focused on your topic or CCAC**
  + I see how focusing the introduction specifically on CCAC guidelines and their ethical considerations would have strengthened the argument from the outset. I’ll work on ensuring more targeted introductions in future assignments.
* **You've already said this in the previous sentence – perhaps focus more on why dignity might be relevant here.**
  + I appreciate the suggestion. While I intended to reinforce the idea, elaborating on why dignity is important in the context of animal ethics would provide a more nuanced explanation. I’ll make sure to develop these points with greater depth in future work.
* **Which sectors are you referring to here? It would be stronger if you named them explicitly.**
  + Naming sectors like agriculture and biomedical research would have made the argument clearer.
* **Make sure you cite this point – you should use academic sources to support your argument."**
  + I’ll ensure that any claims, particularly regarding animal protection laws, are supported by academic sources in future assignments. This will strengthen the validity of my arguments.
* **This is a weak conclusion – perhaps suggest a way forward or expand on how the CCAC can better align with TCPS**
  + A stronger conclusion could include recommendations for how the CCAC can evolve its guidelines. I’ll aim to provide more concrete suggestions in future conclusions.

## 3 minute 1 slide presentation

* I appreciate your comments on the use of color and organization in my slides.
* Incorporating transitions and animations as I introduce new sections is a great suggestion.
  + It would indeed help manage the flow of information better and keep the audience focused on the points I'm discussing at any given moment.
* Regarding the clarity of my stance on animal testing, I see your point about explicitly stating my opinion early in the presentation.
* In future, I will make sure to articulate my position at the beginning to anchor the discussion and provide a clearer framework for my argument.
* I'm also glad you noted the pacing of my presentation.
  + I will work on delivering with more enthusiasm and a conversational tone to avoid sounding too scripted, which should make the presentation more engaging.

## Communications director piece

* I realize the importance of illustrating the economic impact with specific examples. In a similar case, the Biotech Research and Innovation Centre (BRIC) at the University of Copenhagen has been pivotal in generating jobs and stimulating local economic growth. Since its establishment, BRIC has created over 500 new jobs and contributed significantly to the local economy through collaborations with biotech firms and attracting international research funds.
  + <https://www.europabio.org/wp-content/uploads/2021/02/201208_WifOR_EuropaBIO_Economic_Impact_Biotech_FINAL.pdf>
  + <https://www.bric.ku.dk/career-at-bric/jobs_kopi/>
* I appreciate your suggestion to refine the focus of the point regarding scientific knowledge and public awareness
* For the point on making complex science accessible to the public, I'll refer to established programs like the Allen Institute’s public outreach initiatives. They have effectively used simplified language, interactive webinars, and community workshops to demystify complex neurological research for the general public. Drawing on such examples will provide a clearer idea of how our facility can engage with and educate the community effectively.
  + <https://alleninstitute.org/education/>
  + <https://alleninstitute.org/allenimpact/>
* For Con 2 I wanted to focus on the skepticism behind translation to human studies while Con 1 focusing on the ethics behind how animals are treated
  + I see your point about considering other community concerns such as infrastructure impact and displacement of populations due to new constructions. Incorporating these aspects can indeed provide a broader perspective on the community's concerns

## Opinion paper on ethics

* **"Such as?"**
  + I realize that adding specific examples, such as the limitations in areas like neurological research or drug efficacy trials, would have made this point clearer.
* **"What kind of welfare regulations?"**
  + Referring to specific regulations like the use of anesthesia during invasive procedures or the requirement of post-operative care for research animals would have provided more depth.
* **"Reference required for these points. In a graduate program, you are expected to be referencing correctly all of the ideas that are not your own."**
  + I’ll make sure to include proper references in future papers to support my claims and provide academic rigor to my work.
* **"What ethical justifications?"**
  + I was referring to ethical justifications related to the potential benefits of medical advancements for humans, but I should have elaborated. I’ll ensure that I expand on ethical reasoning in future discussions to avoid ambiguity.
* **"This point is a little confusing. You example that you continue to hold the view that animals in medical research should be used if it served medical purposes, however you are less accepting of the idea that animals need to be used?"**
  + I intended to express that while I still acknowledge the necessity of animal research in some cases, I’ve become less accepting of it in situations where alternatives may exist. I’ll work on clarifying my position and making my statements more consistent.
* **"Such as?"**
  + I should have included examples like emerging technologies as alternatives to animal testing. I’ll be sure to provide such specifics in the future.
* **"What ethical standards?"**
  + Referring to specific ethical frameworks, such as the 3Rs (Replacement, Reduction, Refinement), would have made the point clearer. I’ll be more specific with ethical standards in future work.
* **"What are the current standards?"**
  + I should have mentioned existing standards like those set by the Canadian Council on Animal Care (CCAC).
* **"This point kind of comes out of nowhere and isn't a great justification."**
  + I see how this may have seemed abrupt. I’ll ensure that future arguments are more logically structured and better supported.
* **"To state that you continue to hold this view of 'accepted and strongly agreed that the use of animals...' but then discuss how you are not accepting of the idea that 'animals need to be used' is a little contradictory. Stating something along the lines of 'my viewpoint has shifted so that I now believe: xyz' would be better."**
  + I’ll clarify my evolving position by framing it as a shift in perspective, emphasizing that I now believe alternatives should be prioritized unless absolutely necessary

## REB/LOI-C

* **"Why was this not included in your REB application?"**
  + I appreciate the observation and realize that including this information in the REB application would have ensured better alignment with ethical standards. I will make sure to cross-reference such crucial details in future REB applications.
* **"For the purpose of easy comprehension, would have been better to have your inclusion criteria in a list so it is easy to read/understand."**
  + I agree that presenting the inclusion criteria in a list format would make the information more digestible.
* **"Creating a table using the dates and the test/procedures for that day would also make the information more digestible."**
  + A table outlining the schedule of tests and procedures on specific dates would indeed have made the document easier to navigate.
* **"What are vitamin D-related complications?"**
  + I should have elaborated on potential vitamin D-related complications, such as hypercalcemia or kidney issues.
* **"Could have included some creative elements such as the signature lines and acknowledgement sections for the patients."**
  + Including some signature lines and acknowledgment sections would certainly enhance the form’s professionalism and completeness.