Ethics – A cross continental perspective

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Inspiring research

Animals in research

In order to to conduct world-leading research, it is sometimes necessary for animals to be involved. Our research involving animals is undertaken with the highest standards of animal care and is only conducted when there are no feasible alternatives.

The University of Exeter is one of the UK's leading research universities.

At the University of Exeter, some research involving animals is conducted in the fields of animal behaviour and cognition, ecology and conservation, ecotoxicology, immunology and neuroscience.

Our policy is to minimise the involvement of animals in research wherever possible.

Where research involving animals is necessary, the University conducts fieldwork to the highest professional standards, and where the research is conducted on University premises, provides housing and care that equals or exceeds legal requirements.

We are committed to ensuring an excellent culture of care when conducting research with animals, which is underpinned by the principles of the '3Rs' – reduction, refinement and replacement.

All projects involving any animal are reviewed by Ethics Committees whose members include experts in animal welfare.

Every researcher at the University of Exeter working with animals is required to meet the highest ethical and methodological standards and to adhere to the strict legislation in place in the UK to safeguard animal welfare.

These dedicated web pages provide helpful information about research involving animals, both in general terms and at the University.

The official University of Exeter policy on the involvement of animals in research can be viewed on our policy page.

Includes working at institutes outside the UK

- The University wishes to maintain the highest ethical and welfare standards wherever research involving animals is carried out and to ensure that work which would be unacceptable inside the University or under the UK regulatory framework is not conducted elsewhere

- Researchers are expected to meet local ethical standards and regulatory requirements, but also apply UK standards of welfare as far as possible where they are higher. Where this is not possible, researchers will be required to justify the differences in standards during the ethical review process

- Researchers are expected to consider ethical and welfare issues throughout all stages of their work and to make decisions during the work and in the field which are best firstly for researcher safety and secondly for animal welfare

- Where ethical approval for research has been given by one of the following, evidence of approval should be sent to the AWERB and to the relevant College Ethics Committee, and normally no further review should be needed:
  - USA Institutional Animal Care and Use Committee (IACUC)
  - Canadian Council on Animal Care (CCAC)
  - EC member country Ethical Review Process (ERP)
  - Australia/New Zealand Animal Ethics Committee (AEC)

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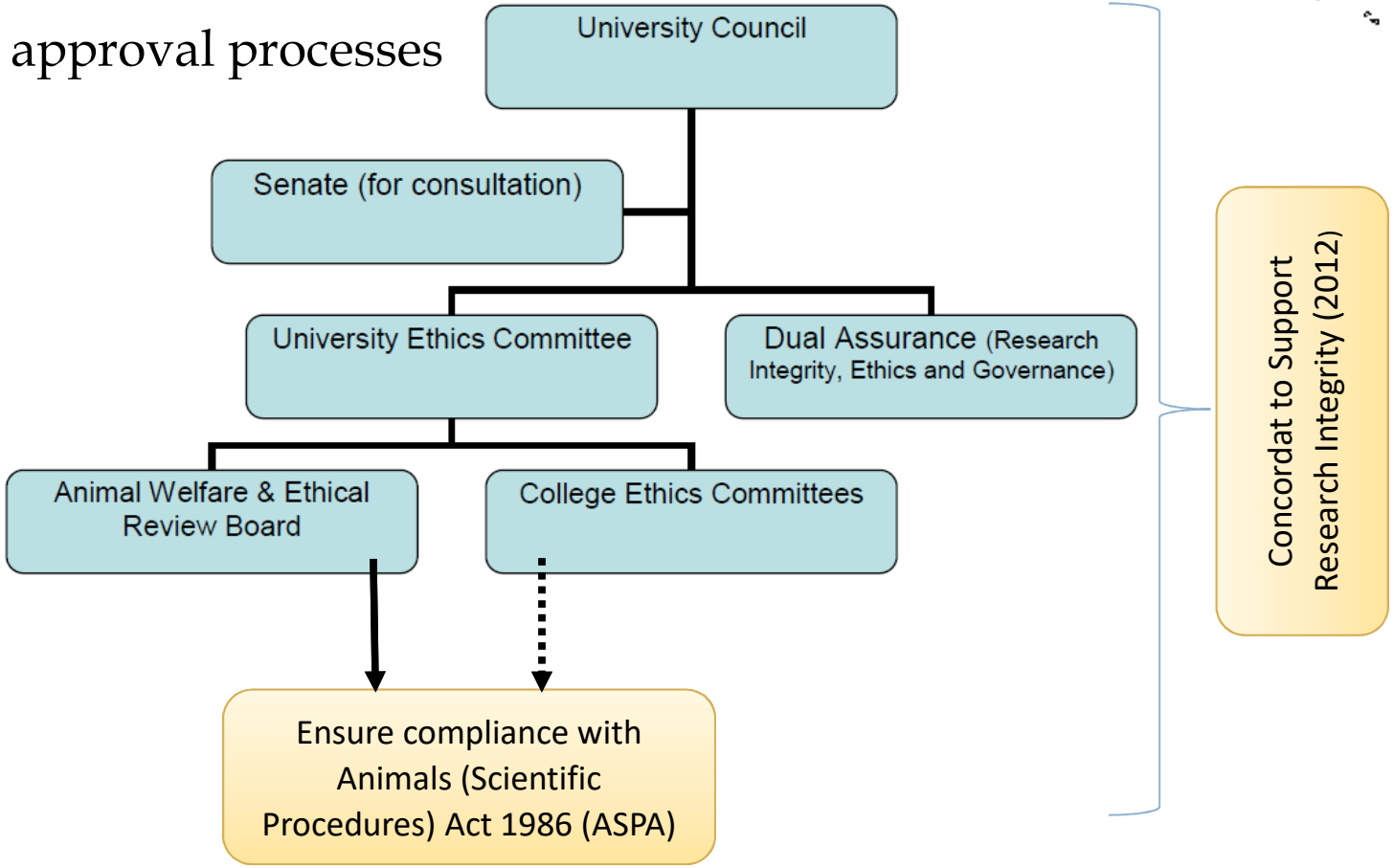
- University approval processes



- Dual assurance – VC executive group develops & manages policy, second member of council ensure due process & consultation

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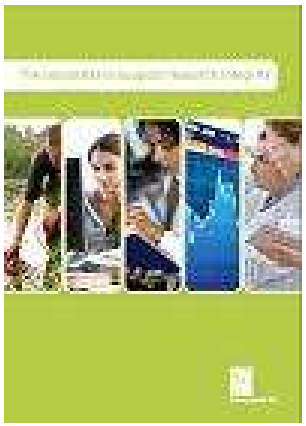
- The Concordat to Support Research Integrity (2012)

This concordat seeks to provide a comprehensive national framework for good research conduct and its governance. As signatories to and supporters of the concordat to support research integrity, we are committed to:

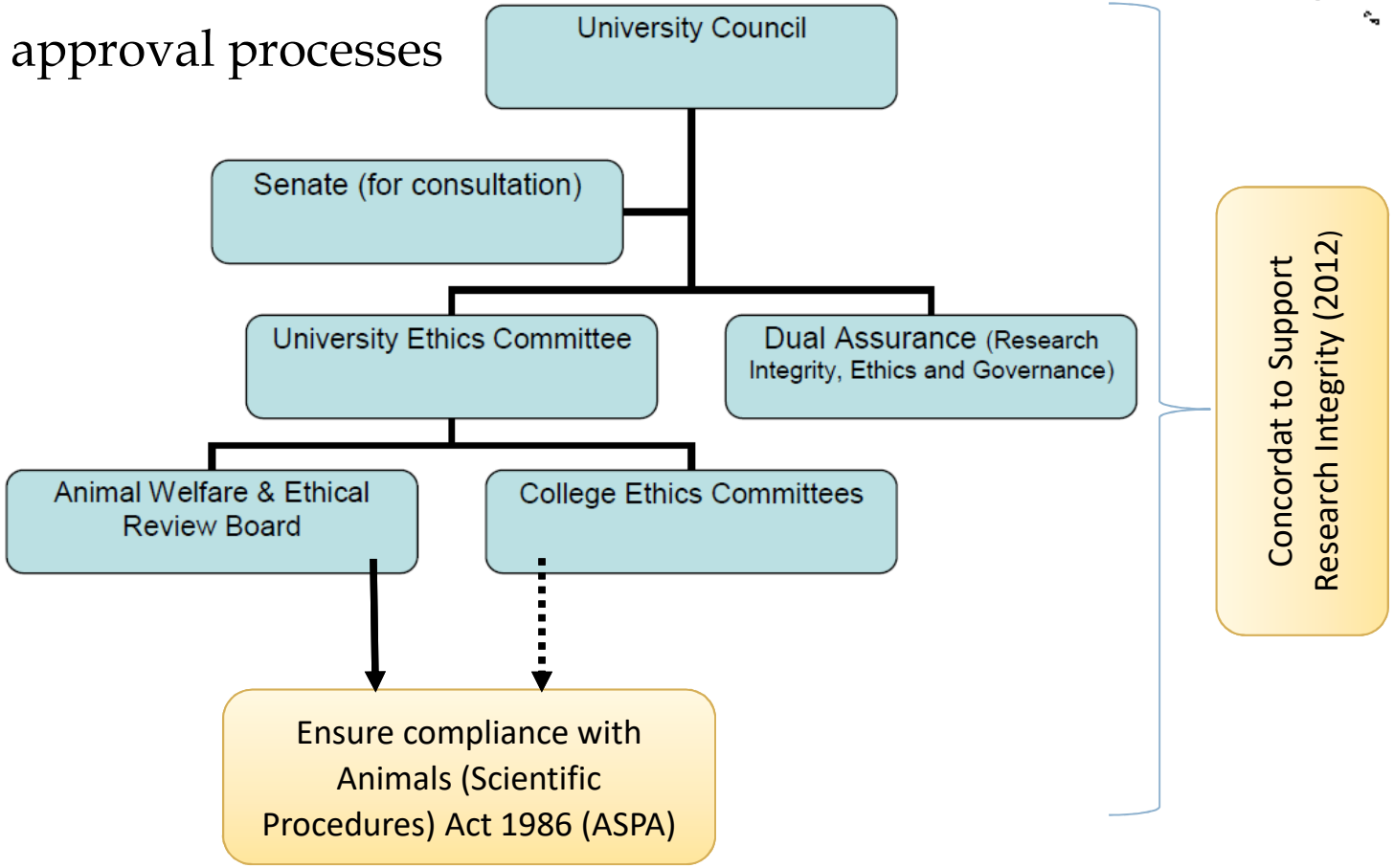


- maintaining the highest standards of rigour and integrity in all aspects of research
- ensuring that research is conducted according to appropriate ethical, legal and professional frameworks, obligations and standards
- supporting a research environment that is underpinned by a culture of integrity and based on good governance, best practice and support for the development of researchers
- using transparent, robust and fair processes to deal with allegations of research misconduct should they arise
- working together to strengthen the integrity of research and to reviewing progress regularly and openly

- Incentives from research councils without which no funding
- Ethical statements in grant applications

Ethics – A cross continental perspective UK

- University approval processes



- Dual assurance – VC executive group develops & manages policy, second member of council ensure due process & consultation

e-Ethics application system: https://eethics.exeter.ac.uk/.

Who should complete an e-Ethics application?

An e-Ethics application must be submitted by all researchers (undergraduate, Masters students, PhD students and all staff). All research involving humans (either living or deceased), their data or tissue, **or animals***, should be ethically reviewed and receive a favourable opinion before work commences

*** All animals – including invertebrates not protected under ASPA**

Applicants must wait for ethical approval **before** commencing any research projects. Ethical approval will not be given retrospectively

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- AWERB designed as a review process specifically for regulated animal work – Named Persons (ELH, NACWO, NTCO, NVS, NIO)
- AWERB – is not just a rubber stamp for project licence applications! – should be a maximum of 40% activity
- Notably a forum for refinements and new techniques to be brought to the attention of researchers
- Most importantly ensuring compliance with ASPA and the 3Rs

AWERB meets every 2-3 months

NVS inspects monthly

Named persons meet every 2 months

HO inspections (unannounced) 2-3/year

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- Animals (Scientific Procedures) Act 1986
  - Cruelty to Animals Act 1849; amended 1876
- Protected animal "…all living vertebrates, other than man, and any living cephalopod. Fish and amphibia are protected once they can feed independently and cephalopods at the point at which they hatch……embryonic and foetal forms….last third of gestation
- Regulated procedure "…A procedure is regulated if it is carried out on a protected animal and may cause that animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by inserting a hypodermic needle according to good veterinary practice
- ASPA is a criminal act and so can be enforced by prosecution through the courts for offences against this law

Animals (Scientific Procedures) Act 1986

Parliament of the United Kingdom

Long title	An Act to make new provision for the protection of animals used for experimental or other scientific purposes.
Citation	1986 c. 14
Territorial extent	England and Wales; Scotland; Northern Ireland
Dates	
Royal assent	20 May 1986
Commencement	1 January 1987 (part) [1] 1 January 1990 (full)

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- Animals (Scientific Procedures) Act 1986
- 3 levels of regulation
  - Place – (Establishment Licence Holder)
    - building is fit for purpose (infrastructure, staff, equipment), leadership, compliance, 3Rs, ensure no conflicts of interest, signs off project licences
  - Project – (PPL)
    - Details purpose, all experimental plans and procedures, harm/benefit analysis, responsible for all work under their licence, ensure students/staff are competent in all techniques
  - Person – (Personal individual licence)
    - Primarily responsible for the daily care and welfare of the animals during their experiments, appropriate labels, daily records, report severity issues immediately
  - Schedule 1 register for humane killing
    - Trained and competent to euthanise an animal
  - Maintenance licence?

Home Office

Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes

Ethics – ASPA Legislation: Standard Conditions UK

Training and Competency

STANDARD CONDITION 17 (PIL): In order to ensure that regulated procedures are performed competently, the licence holder shall not apply regulated procedures to an animal unless given the appropriate level of supervision by the project licence holder or an experienced personal licence holder deputed by him/her for such time as may be needed to achieve competence

PIL holder can move between project licences as long as they are competent but NOT animals

As an experienced PIL holder, working at the University of Exeter, I can confirm that I am trained and competent in the following licenced procedures (as of the date of this letter) and have recent (within the last two years) relevant experience in performing these procedures:

Procedure	Anaesthesia#	Species	Date last performed	Reassessment required? (NTCO use only)
Schedule 1 (terminal anaesthesia and pithing)	AC	Zebrafish, Stickleback, Rainbow trout	Aug 2017	
Blood sampling from caudal blood vessels	AB	Rainbow Trout	Mar 2017	
Intramuscular injection of pit tag tracker	AB	Rainbow Trout	Mar 2017	
Embedding of embryo-larval stages in agarose or methylcellulose for microscopic and video image analysis	AB	Zebrafish	Aug 2017	
De-chorionation of fish embryos	AA	Zebrafish	Aug 2017	
Assessment of critical swimming speed in swim flume	AA	Zebrafish	June 2017	
Breeding and maintenance of genetically modified zebrafish.	AA	Zebrafish	Jan 2018	
Breeding and maintenance of wild-type zebrafish	AA	Zebrafish	Jan 2018	
Chemical exposure testing	AA	Zebrafish, Stickleback, Rainbow trout	Aug 2017	

Add lines as required.

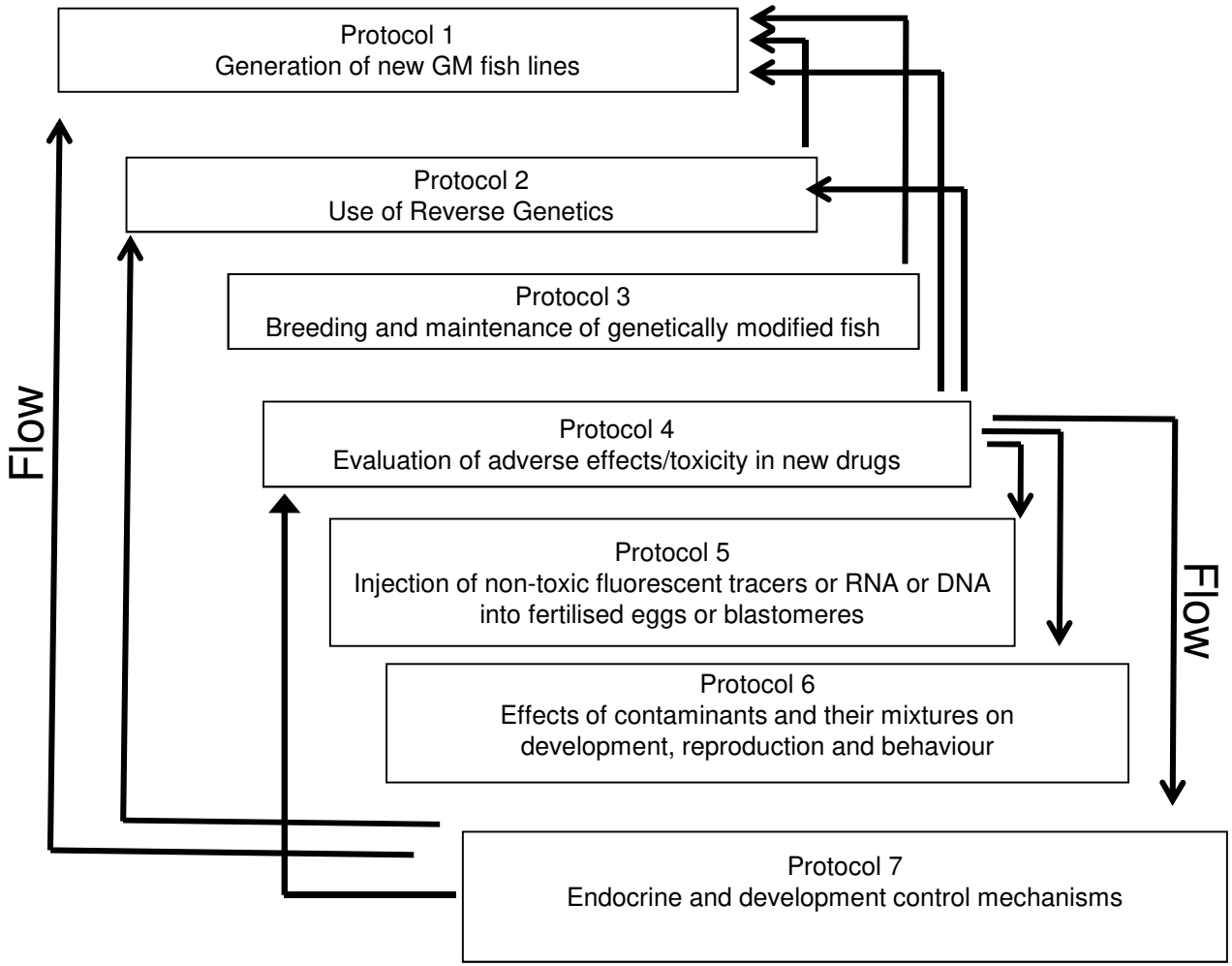
#AA – none, AB – local or general, AC – terminal

Non ASPA Animal Training

- You can also use your training record to record non- procedural tasks with animals
  - Handling
  - Restraint
  - Health checking
  - Trapping/ catching
  - Identification

All of these are important for good animal welfare

Ethics – ASPA Legislation: Standard Conditions UK



Protocol No.	Estimated numbers over the duration of the project	Severity limit
1	Adults (500), juveniles (2000) and embryos (2000) per year	moderate
2	Adults (400), juveniles (600) per year	Mild
3	Adults (100), juveniles (100) per year	moderate
4	2000 per year	severe
5	500 per week	Mild
6	500 per year	Mild
7	2000 per year	Moderate

Animals undergoing scientific procedures should be inspected at a frequency commensurate with the severity!

Home Office

PPL Standard Condition 18 Notification Form

Please use this form to notify the Animals in Science Regulation Unit (ASRU) of procedural-related adverse effects that have exceeded or are likely to exceed the severity limitations or controls described in the project licence. ASRU will use this information to determine whether any further action is required.

Do not use to report:

- adverse effects that are due to non-procedural issues;
- potential non-compliance (report by other means);
- issues without adverse welfare consequences.

If you are in doubt whether or not you need to fill in this form, please contact your assigned Inspector.

Please clearly title your document: **'ASRU_establishment name_PPL number_PPLh surname_date_sc18'** and send to your Inspector (e.g. using cjsm) with the subject heading 'PPL SC 18 Notification PPL [Number]

Establishment Licence name	
Establishment Licence number	
Name of PPL holder	
PPL number	
Protocol no	
Protocol title	
Severity classification	

1. Date of incident	
2. Species	
3. Brief details of study and how the limits or constraints have been breached	
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	
5. Cause of Problem, if known	
6. Action that has been or will be taken *(For example, formulation of drug changed, supportive treatment given, study design modified). If no action needed, indicate why (for example, none required as study has been terminated and will not be repeated)*	
7. Reported by (name)	
8. Date	

**********For official use**********

Inspector's comments and recommendations:

Comments and recommendations	
Inspector name	
Date	

Ethics – A cross continental perspective UK

- NC3Rs

Definitions of the 3Rs	Standard	Contemporary
Replacement	Methods which avoid or replace the use of animals	Accelerating the development and use of models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals
Reduction	Methods which minimise the number of animals used per experiment	Appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base
Refinement	Methods which minimise animal suffering and improve welfare	Advancing research into animal welfare by exploiting the latest *in vivo* technologies and by improving understanding of the impact of welfare on scientific outcomes

- https://www.nc3rs.org.uk/the-3rs - overview of the 3Rs
- https://www.nc3rs.org.uk/3rs-resources - NC3Rs resources page
- https://www.nc3rs.org.uk/experimental-design - resources for experimental design
- https://www.nc3rs.org.uk/arrive-guidelines - for researchers reporting the results of their animal research studies – maximise information published & thus minimise unnecessary studies
- https://www.nc3rs.org.uk/news/introductory-training-3rs-time-fresh-approach - training video

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- The Concordat on openness is at http://concordatopenness.org.uk/
- Universities Federation on Animal Welfare - welfare information and a small grants scheme https://www.ufaw.org.uk/
- Fairsharing – curated resource for data standards, policies and databases (particularly good for life and biomedical sciences); https://fairsharing.org/
- Equator network - reporting guidelines and toolkits for health-related research http://www.equator-network.org/

Ethics – A cross continental perspective

- How as facility managers/husbandry staff can we help?
  - Planning – study request form to ensure compliance, oversite on competency, appropriate care, prevent over production, learn from past studies
  - Establish ring tests between facilities to approve husbandry practices/protocol
  - Standardise/optimize our approaches
- Publish accurate methodology on fish husbandry

Canada's take

- Cornerstone of the Ethics guidelines in Canada:
  - 3Rs
  - Animal Care Committees (= AWERB and IACUCs)
  - Animal care standards and guidelines

The use of animals in research, teaching, and testing is acceptable only if it promises to contribute to understanding of fundamental biological principles, or to the development of knowledge that can reasonably be expected to benefit humans or animals.

Animal Care Committees

- Composed of (at least):
  - 1 scientist who works with animals
  - 1 institutional member who does not work with animals
  - Veterinarian
  - Community representative
- Responsibilities:
  - Annual review of all animal use protocols (AUPs)
  - Annual facility inspections
  - Post-approval monitoring of AUPs
  - Training of personnel

CCAC Site Visits

- 3-year program reviews
  - Full and interim visits
- Rely on program description and CCAC guidelines and standards
- Approval provides a Certificate of Good Animal Practice®
  - Required to receive funding from federal granting agencies

Provincial Regulations

- Ontario
  - Only province to have an Animals for Research Act
  - Mandated unannounced inspections ~annually
- Other provinces
  - Some refer to CCAC regulations
  - Many have provincial funding agencies that require CCAC certification
  - No universal regulations across provinces

Hierarchy of Oversight – Federal Level

Historical Background of the Rise of Animal Research Oversight in the United States

Pre 1963 - regulation was conducted solely by investigators, and research laboratories had inconsistent animal care policies and standards of care.

1961 – Group of veterinarians formed the Animal Care Panel

1963 - The Animal Care Panel publishes the first edition of “The Guide for Care and Use of Laboratory Animals.

1966 - Life Magazine expose on mistreatment of animals in research is published

1966 – Congress passes the Laboratory Animal Welfare Act (USDA assigned as the responsible agency)

Hierarchy of Oversight – Federal Level

U.S. Dept. of Health and Human Services (DHHS)

- Agency for Healthcare Research and Quality (AHRQ)*
- Agency for Toxic Substances and Disease Registry (ATSDR)*
- Centers for Disease Control and Prevention (CDC)*
- Food and Drug Administration (FDA)*
- Health Resources and Services Admin. (HRSA)*
- Indian Health Service (IHS)*
- National Institutes of Health (NIH)*
- Substance Abuse and Mental Health Services Admin.

PHS Policy on Humane Care and Use of Animals (1971)

U.S. Government Principles for the Care of Vertebrate Animals Used in Testing, Research and Training

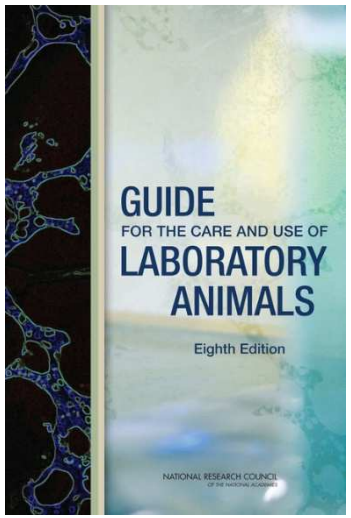
Health Research Extension Act (1985)

-Establish guidelines
-Animal welfare assurance mechanism (OLAW)
-Internal Animal Care and Use Committee (IACUC)
-Reporting of noncompliance and deficiency correction

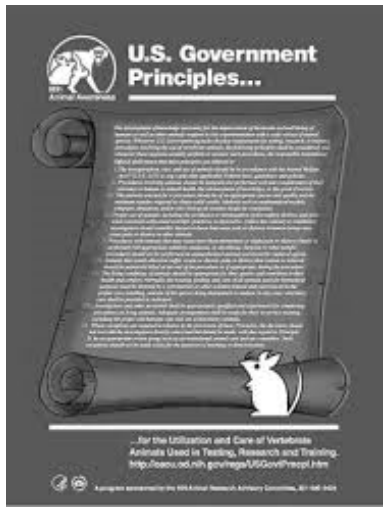
OLAW – Mission Statement and Guidance

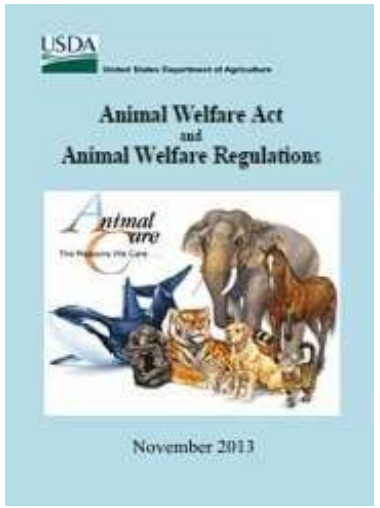
Mission Statement:

The Office of Laboratory Animal Welfare (OLAW) provides guidance and interpretation of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals, supports educational programs, and monitors compliance with the Policy by Assured institutions and PHS funding components to ensure the humane care and use of animals in PHS-supported research, testing, and training, thereby contributing to the quality of PHS-supported activities



AVMA Guidelines for the Euthanasia of Animals



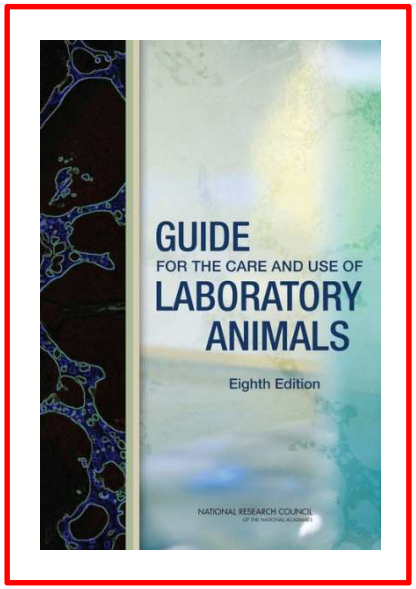


OLAW – Mission Statement and Guidance

The “Guide”

8th Edition specifically mentions aquatic species (2011)

- Pages dedicated to “aquatic species” = ~10
- Contains few mandates/directives regarding care



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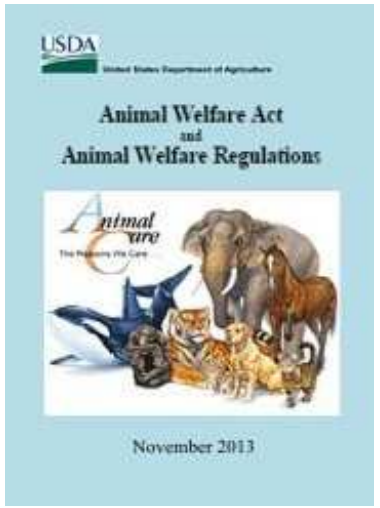
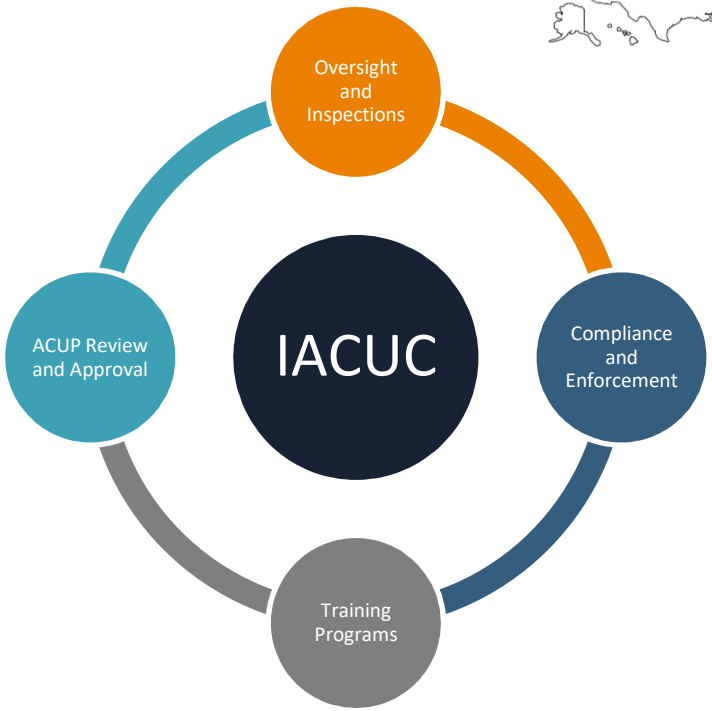


Oversight at the Institutional Level



Office of Research

Office of Research Integrity

Internal Animal Care and Use Committee (IACUC)

Veterinarian (Lab Animal and Aquatic)

Facility

Users submit ACUP proposals directly to IACUC for review and ultimately approval or denial

Oversight at the Institutional Level

- Chief Executive Officer
- Veterinarian with training or experience with experimental animals
- Someone with no relation with the institution except for serving on the IACUC
- Scientist with experience using experimental animals
- A nonscientist.

Office of Research

Office of Research Integrity

Internal Animal Care and Use Committee (IACUC)

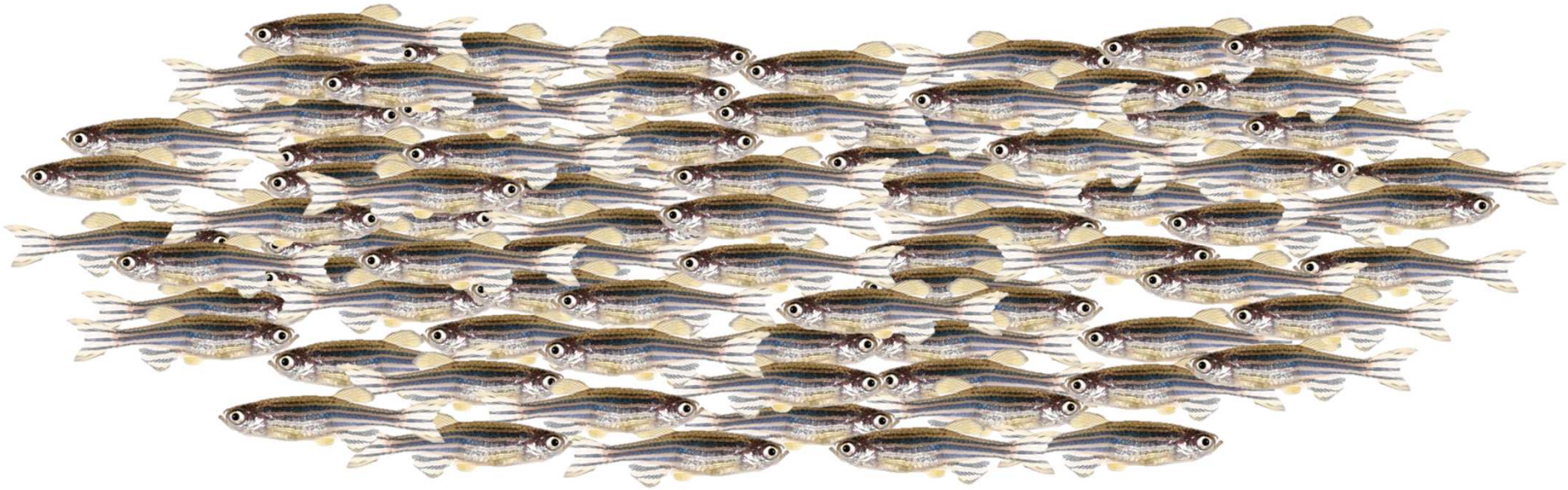
Veterinarian (Lab Animal and Aquatic)

Facility

Users submit ACUP proposals directly to IACUC for review and ultimately approval or denial

Common Ethics Problem in the USA

Overproduction and Excessive Accumulation of Fish



Focus on Improving Ethics Standards

- NC3Rs

	Standard	Contemporary
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Reuse???

Overproduction – Causes

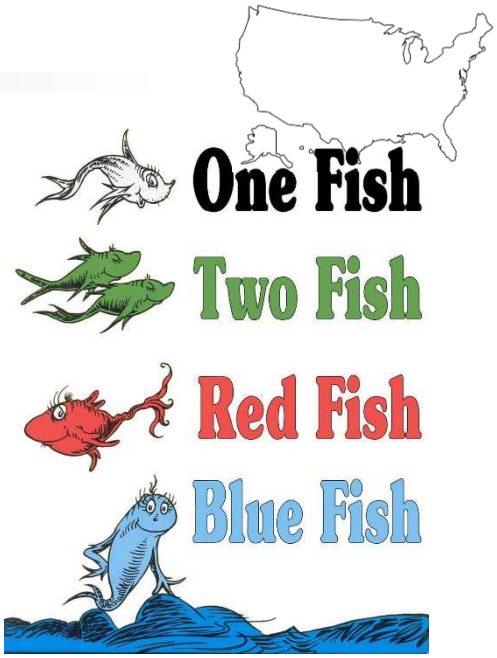
The attributes that make zebrafish an attractive research model are also largely the reason that hoarding and over production are such a problem!

They are:

- Small
- Easy to care for
- In some cases cheaper ($0.48 per tank per day vs $0.78 per box per day)
- Higher stocking density
- You can make a lot of them fast

Would you make 250 zebras if you only needed 25?

Excessive Accumulation - Causes



Why do people end up with too many fish?

Excessive line accumulation

That's a cool line, we should get it in case it's useful!

Unwillingness to euthanize old fish

But I just need to keep them until I get my reviewer comments back!

I'm keeping the old fish as back up in case something happens to my fish.

Keeping lines not being used for current research (nostalgia)

I know I haven't used the line for two years…..but I might?

Over ambitious students!

Starting too many projects at one time with no clear order or plan

The Problems

Why isn't this caught by oversight groups?

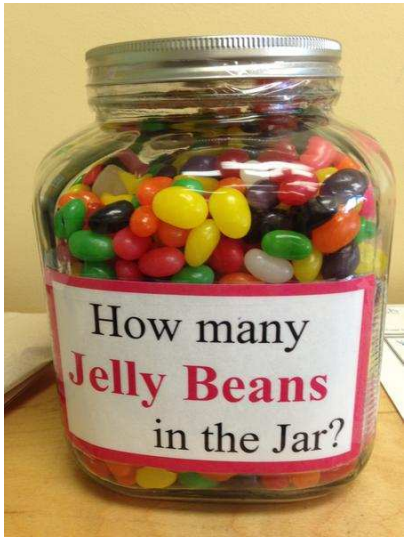
Zebrafish are more tolerant of things like overcrowding

⇩

Census and survey information is harder to gather

⇩

Makes verifying fish population numbers more difficult



Solutions

1. **SARL Stock ACUP**
   (Animal Care and use Protocol)
2. **Active/Dormant Status**
3. **Experimental Design Consultation**
4. **Reuse of Animals**

Facility ACUP

Facility ACUP

-all animals (larval exposure is the exception) are raised on the SARL Stock ACUP

-sets husbandry standard for all animals in the facility

-specified # of animals transfer to the project ACUP when the research starts

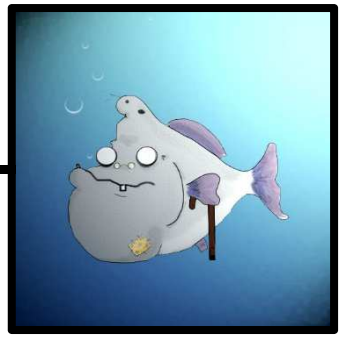
-excess animals remain on the facility ACUP and are repurposed

Project ACUP can ask for special condition outside the Facility ACUP

-allows for special husbandry or age considerations for study fish

-project ACUP must specify any major deviations from standard care or age

This helps prevent accumulation of old fish!



Line Maintenance Strategies

Active vs dormant lines:

-lines currently being used in a research project are on full maintenance

-lines not used within the last 12 months move to dormant status

Active

Next generations in the preferred zygosity are made every 4-6 months or as needed to support the research

Embryos can be requested at any time with 48 hours notice

Dormant

Population will be downsized (2 tanks, equal male/female)

New stock will be generated every ~8-9 months in limited quantities to maintain the line

Embryos can be requested, but numbers will be limited

If large numbers are needed for a study, the line will be taken out of dormant status

Setting the Users Up for Success

By reviewing an experimental design prior to the production of fish (by the user or the facility), you have the opportunity to teach the user valuable information that can reduce overproduction.

- average survival rates
- differences between facilities
- age limitations
- growth rates

This is also an opportunity to identify problems!

- procedure optimization
- if the N is 25, why did the user request 200 fish?

Is there a 4th R that can be considered?

REUSE
When possible, using the same set of animals to achieve multiple goals within an institution.

SCENARIO
SARL produces large numbers of wild type fish for use in high throughput screening projects.

- housing and husbandry are standardized
- due to SPF requirements, fish are euthanized after 1 year

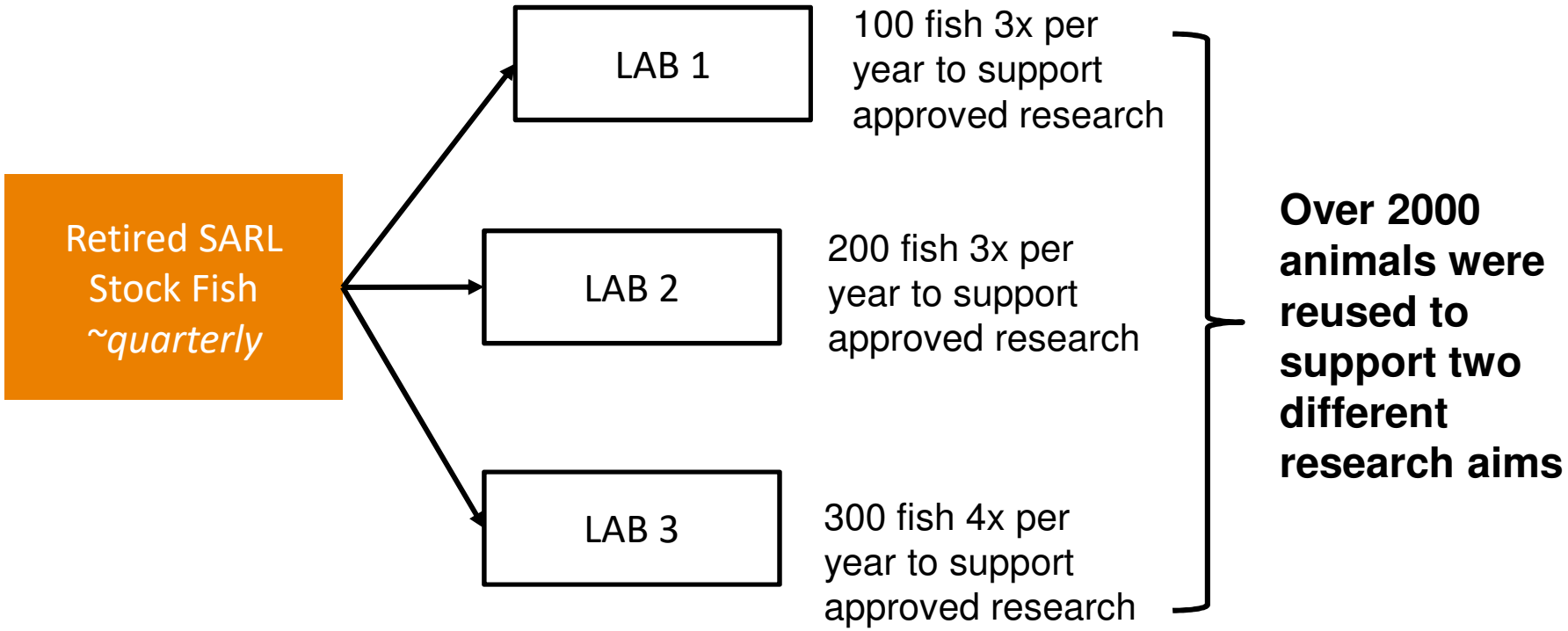
Several satellite labs on campus require fish stocks that are 1 year of age for a variety of research purposes.

- infectious disease studies
- nutrition studies

Is there a 4th R that can be considered?

REUSE

When possible, using the same set of animals to achieve multiple goals within an institution.



End Result?

By address the main causes of over accumulation of fish, through constructive avenues focusing on education, guidance and fish management, both the facility and the researchers can accomplish their