VIRTUAL IACUC 101 PLUS

PROTOCOL REVIEW AND APPROVAL CRITERIA Part 1

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Outline

- Role of the IACUC
- Proactive protocol review
- Methods of IACUC review
- IACUC protocol approval criteria
- Conclusion

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ROLE OF THE IACUC

Society's Gatekeeper

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The IACUC

The responsible advancement of science and medicine depends upon the use of animals in scientifically important and humanely conducted research reviewed, approved and monitored by IACUCs that work in partnership with the investigator and the institution.

4

PROACTIVE PROTOCOL REVIEW

The PI is the IACUC's Customer

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IACUC Review Recommendations

- Consider the position and pressures of being a PI.
- Use FCR, DMR and VVC in consideration of protocol complexity, invasiveness and efficiency.
- Make protocol review a facilitative and educational process for the PI.
- Don't ask for more information than needed.

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IACUC Review Recommendations *Cont'd*

- Practice the concept of reasonable protocol flexibility.
- Ensure IACUC reviews are consistent for each PI and across PIs.
- Engage in constructive dialogue with the PI during the review process.
- Ensure IACUC review letters are succinct, understandable and diplomatic.

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METHODS OF IACUC REVIEW

Choose the Best Method that Fits the Protocol

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Designated Member Review (DMR)

- At least one qualified IACUC member serves as the designated reviewer (DR) and conducts the DMR.
- The DR is appointed by the IACUC Chair.
- All IACUC members must be given (at least) a list of protocols with written descriptions available.
- DMR begins only after all IACUC members have had an opportunity to review the protocol and call for FCR, if warranted.

PHS Policy IV.C.2; 9 CFR 2.31(d)(2)

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DMR *Cont'd*

- IACUC members do not vote in DMR and, other than the DR, cannot require modifications.
- The DR may approve or require modification of the protocol (*to secure approval*) but cannot disapprove it.
- If DMR involves more than one reviewer, consensus must be achieved.

PHS Policy IV.C.2; 9 CFR 2.31(d)(2)

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Full Committee Review (FCR)

- A convened face-to-face meeting is preferable for complex, invasive protocols.
- Use real-time electronic communication when necessary.
- Ensure presence of a quorum (*simple majority*).
- Approval, require modification (*to secure approval*) or disapproval requires a simple majority vote.

PHS Policy IV.C.2; 9 CFR 2.31(d)(2)

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Review of a Modified Protocol after Initial FCR

- Re-review at a subsequent FCR meeting
- Re-review by DMR using either of the following methods:
  - Classic
    - All IACUC members are given the option of calling for FCR.
  - DMR subsequent to FCR
    - IACUC members at the initial FCR *unanimously* agree to allow DMR of the revised protocol, in accordance with an IACUC policy.

NOT-OD-09-035, January 8, 2009

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Use of DMR vs. FCR

Consider having a policy specifying research categories which require FCR or are eligible for DMR based upon the anticipated impact of procedures on animal well-being.

DMR	FCR
▪ Non-survival surgery	▪ Major Survival surgery
▪ Tissue collection	▪ Radiation sickness
▪ Antibody production	▪ Tumor inducement
▪ Telemetry	▪ Toxicology
▪ Animal behavior obs.	▪ Infectious disease
▪ ….	▪ ….

Note: The PHS Policy and USDA Regulations do not prescribe research categories which require FCR.

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IACUC Review of Significant Changes

- Changes which require review and approval by either DMR or FCR (classic methods)
- Changes which are eligible for Veterinary Verification and Consultation (VVC)
- Changes which are eligible for administrative handling (AH)

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Classic Methods vs. VVC

Requires FCR or DMR	Eligible for VVC	Eligible for AH
Nonsurvival to survival surgery	Changes in anesthesia, analgesia, sedation, experimental substances	Increase in previously approved number of animals
Increase in pain, distress, or invasiveness	Change in AVMA-approved methods of euthanasia	Change in personnel (other than the PI)
Change in study objectives	Change in duration, frequency, type or number of procedures	Correction of typographical and grammatical errors
Change in Principal Investigator		Contact information updates
Change which impacts personnel safety		
Change in housing or use of animals in a location not overseen by the IACUC		
Change in species		

PHS Policy IV.C.2; NOT-OD-14-126, August 26, 2014

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Continuing Review

- Use a continuing review form with a *progress report* that includes the status of the research and unanticipated problems (technical, AEs, mortality).
  - PHS Policy: Complete (de novo) re-review of the project *no less* often than once every 3 years.
  - USDA: Complete (de novo) re-review of the project *no less* often than once every 3 years.
  - Consider using DMR for protocols subject to continuing review without animal welfare issues or other problems.

PHS Policy IV.C.5; The Guide, p. 34; 9 CFR 2.31(d)(5); Amended AWAR, effective 12/27/21, 86 FR 66919 (11/24/21)

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IACUC PROTOCOL APPROVAL CRITERIA

Ask the Right Questions with Corresponding Approval Criteria

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SECTION I

Scientific Aims

The Why

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IACUC Approval Criteria

- The proposed research is supported by key background information (published and unpublished).
- The specific aims of the research are clear and judged to be achievable.
- There is no unnecessary duplication of experiments as attested to by the PI and explained as necessary.

9 CFR 2.31(d)(1)(iii); The Guide, pp. 25-26

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SECTION II

Animal Subjects

A Scientifically Appropriate Species with the Required Biological Characteristics is Critical

20

IACUC Approval Criteria

The specific aims of the research cannot be achieved using non-animal models (*replacement*).

PHS Policy IV.D; USGP III; 9 CFR 2.31(d)(1); The Guide, pp. 5, 12, 25-26; NOT-OD-16-006, October 13, 2015

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IACUC Approval Criteria *Cont'd*

- The animal subjects are a scientifically appropriate species and strain with the required biological characteristics:
  - Sex
  - Age
  - Weight
  - Health Status
  - Genetic Background
  - Source

PHS Policy IV.D; USGP III; 9 CFR 2.31(e)(1,2); The Guide, p. 25 NOT-OD-16-006, October 13, 2015

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IACUC Approval Criteria *Cont'd*

The animal subjects are the lowest species on the phylogenetic scale that are scientifically appropriate (*relative replacement*).

USGP III; The Guide, p. 5; OLAW Guidance on the NIH VAS, May 13, 2021

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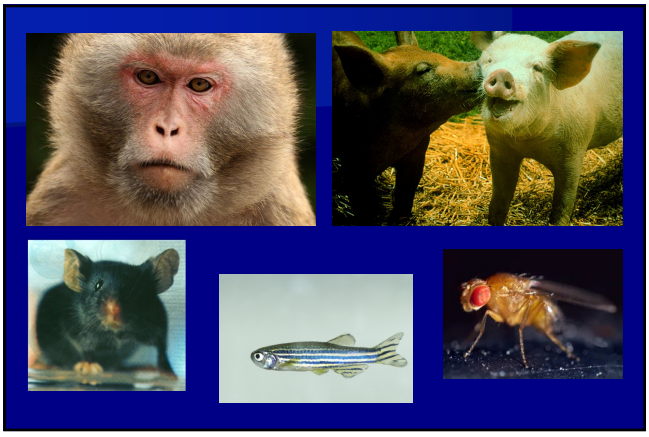

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SECTION III

Scientific Elements

A Flawed Experimental Design Equals Invalid Research

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NIH OLAW

"The PHS Policy and The Guide expect the IACUC to consider whether the research design is sound."

Lab Animal Vol. 49: 29-31, 2020

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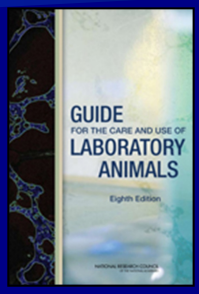
The Guide

"…the IACUC … should evaluate scientific elements of the protocol…. For example, hypothesis testing, sample size, group numbers and adequacy of controls…."

The Guide, p. 26



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AAALAC

"Scientific rigor and experimental reproducibility directly impact the welfare and number of animals used in research …. The IACUC review should confirm [*based on an initial review by a grants panel or as an assigned responsibility to the committee*] that the protocol contains pertinent study design elements … including randomization, blinding and controls."

AAALAC FAQ on Scientific Reproducibility, 2021

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IACUC Approval Criteria

- The research design is judged to be scientifically sound *(based, in part, on SRG, or other, peer review panel)* and is consistent with the specific aims of the research.
- Procedures involving animals are sufficiently described and congruent with the specific aims.
- Procedures are designed to ensure animals will experience the least possible pain, discomfort or distress.
- The number of animals to be used (experimental and control groups) is specified and fits the research design.

PHS Policy IV.D.1.d.; USGP III; The Guide, pp. 25, 27; NC3Rs-EDA; 9 CFR 2.31(e)(3)

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IACUC Approval Criteria *Cont'd*

- The number of animals required is the *minimum* necessary to obtain valid results based on sound statistical/scientific justification (*reduction*).
- The experimental and humane endpoints are closely linked and scientifically sound (*refinement*).

USGP III; The Guide, pp. 27-28; 9 CFR 2.31 (d)(1)(iii)

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SECTION IV

Potential Benefit

No Benefit – No Research

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OPRR-AWD

"The primary focus of the SRG is scientific merit whereas the primary focus of the IACUC is animal welfare. It is evident, however, that there is… overlap of function between the two bodies… The IACUC is expected to… consider in its review the general scientific relevance of the proposal."

ILAR News 33 (4): 68-70 (1991); USGP II

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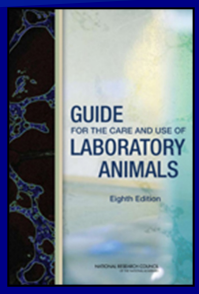
The Guide

"Using animals in research is a *privilege* granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being."

The Guide, p. 4.



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NIH

"The primary role of SRGs is addressing scientific merit while IACUCs focus on evaluating animal welfare … These functions are not mutually exclusive because it is not entirely possible to separate scientific value from animal welfare …."

NOT-OD-22-005, October 18, 2021

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SECTION IV *Cont'd*

Potential Benefit
No Benefit – No Research

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NIH

- "… peer review by SRGs is not intended to supersede or substitute for IACUC review and approval …."

NOT-OD-22-005, October 18, 2021

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IACUCs Have the Last Word

- Regardless of whether the SRG, or other peer review committee, assigns a grant application a high priority score indicative of sufficient merit to warrant funding, it is ultimately the responsibility of the IACUC to determine:
  - There is sufficient potential benefit to justify use of the animals

    AND
  - The research, as described in the protocol, is humane and in compliance with all applicable federal requirements

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IACUC Approval Criteria

- The *potential* benefit (*scientific merit/value*) of the research is congruent with the specific aims.
- There is a *reasonable* expectation that the research will (in the short term or long term)
  - lead to improvement in human and/or animal well-being
  - provide significant new knowledge, or
  - contribute to the good of society.

PHS Policy IV.D.1.d;
USGP II; The Guide, p. 4.

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SECTION VI

Refinement

A Key to Ethical Research

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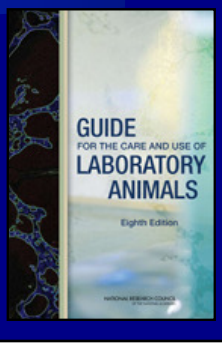
The Guide

"…the three Rs have become an internationally accepted approach for researchers to apply when deciding to use animals in research and in designing humane animal research studies."

The Guide, p. 5



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Refinement Defined

- "Refinement refers to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress …"
- "Refinement and reduction goals should be balanced on a case-by-case basis."

The Guide, p. 5.

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IACUC Approval Criteria

- Husbandry is species-specific and designed to enhance animal well-being. Any deviations are scientifically justified.
- Procedures will be used that have the least amount of potential PDDMM in consideration of any justifiable scientific constraints.

USGP IV; 9 CFR 2.31(d)(1); The Guide, pp. 5, 12, 26

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IACUC Approval Criteria *Cont'd*

- The PI has provided a written narrative describing the methods and sources used to determine that no alternatives to procedures that may cause more than momentary or slight pain or distress were scientifically feasible (*AWAR requirement*).
  - Literature database(s) searched (usually at least 2) or other sources consulted (i.e., named expert),
  - The date of search, years covered, and key words,
  - Reduction, replacement and refinement (all "3 Rs") are addressed.

USDA 9 CFR 2.31(d)(1); "AWIC" htpp://www.nal.usda.gov/awic

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IACUC Approval Criteria *Cont'd*

- The PI has provided an explanation why any alternatives described in the current peer reviewed scientific literature cannot be used to achieve the specific aims of the research.

PHS Policy IV.D.1.b; USGP III

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Examples of Refinement

- Less invasive procedures
- Fewer invasive procedures
- State of the art pain relief
- Less restraint time
- …
- Environmental enrichment
- Highly attentive monitoring
- More humane euthanasia
- Use of humane endpoints
- …

Applies to all species, as appropriate

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SECTION VII

Animal Pain, Distress, Discomfort (AEs)

Timely Identification of Anticipated and Unexpected AEs is Essential

47

IACUC Approval Criteria

- The nature, magnitude, and duration of any anticipated AEs are adequately described *and* consistent with known effects of the procedures applied to the species involved in the research. AEs are:
  - more than momentary or slight pain or distress
  - more than minor discomfort
  - cumulative AEs
  - other
- The initially assigned USDA pain categories (B, C, D, E), as applicable, fit the protocol.

9 CFR 2.31(d)(IV);
The Guide, pp. 120-121

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SECTION VIII

Treatment of Pain or Distress

An Ethical and Regulatory Based Imperative

49

IACUC Approval Criteria

- The regimen to treat anticipated pain, discomfort or distress involves use of appropriate state of the art sedation, analgesics, and anesthesia administered pre-operative, intra-operative and post-operative, as necessary, based upon:
  - Nature and length of procedures
  - Species and strain
  - The anticipated pain, discomfort or distress
  - Safety of the agent
- Any withholding of pain-relieving agents or use of neuromuscular blockers is clearly justified for compelling scientific reasons.

The Guide, pp. 26, 121-123; PHS Policy IV.C.1.b; 9 CFR 2.31(d)(1); Recognition and Alleviation of Pain in Laboratory Animals (NRC 2009a)

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SECTION IX

The Humane Endpoint

A Critical Component of Refinement

51

IACUC Approval Criteria

- The humane endpoint is the earliest possible point at which pain and distress are prevented, terminated or relieved.
- The experiment is designed so that the experimental and humane endpoints are closely linked.
- The species-specific humane endpoint assessment criteria are appropriate.
- The action(s) to be taken upon reaching the humane endpoint is acceptable.

USGP VI; The Guide, pp. 27-28; 9 CFR 2.31(d)(1)(v)

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SECTION X

Post-Procedure Monitoring

Inadequate Monitoring Compromises Animal Welfare

53

IACUC Approval Criteria

- The monitoring plan, including frequency of evaluation and health status criteria, is appropriate based upon:
  - The nature of the intervention(s)
  - The species
  - The magnitude of anticipated pain, discomfort, or distress
  - The duration of anticipated pain, discomfort, or distress
  - Possible complications
  - The need to recognize when the humane endpoint is reached

PHS Policy; 9 CFR 2.33(b)(5); The Guide, pp. 28, 119-120

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SECTION XI

Mechanical Restraint

It's Not Just a Convenience in Handling Animals

55

IACUC Approval Criteria

- Use of the restraint device is justified.
- The animals will be conditioned to the restraint device.
- The restraint device will allow normal postural adjustments.
- The duration of restraint is minimized.
- The animals will be monitored appropriately.
- Animals that do not adapt to the restraint device will be removed.

The Guide, pp. 29-30

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SECTION XII

Altered Living Conditions

It's Not Just What is Done to Animals, but How They Must Live

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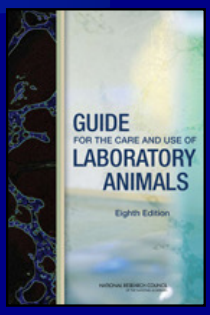
The Guide

"The primary aim of environmental enrichment is to enhance animal well-being by providing animals with… structures and resources that… promote psychological well-being."

The Guide, p. 52



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IACUC Approval Criteria

- Any departure from species-appropriate living conditions, as set forth in The Guide, applicable USDA Regulations, or that are medically necessary, must:
  - Be fully justified
  - Provide animals with as much choice and control over their environment as possible
  - Provide as much environmental enrichment as possible

The Guide, pp. 41-103; PHS Policy IV.C.d; USGP VII; 9 CFR SUB A-F

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SECTION XIII

Euthanasia

The End of an Animal's Involvement in Research is as Important as the Beginning

60

IACUC Approval Criteria

- The method(s) of euthanasia complies with current AVMA Guidelines, based upon:
  - The specific aims of the research
  - The species, size and age of the animal
  - A minimum of pain and distress associated with the method
  - Ability to quickly produce a loss of consciousness
  - Legitimate logistical considerations
  - Safety of personnel
- Deviations from the AVMA Guidelines are scientifically justified
- The method to confirm death is appropriate

PHS Policy IV.C.1.g; 9 CFR 2.31(e)(5); The Guide, pp. 123-124; AVMA Guidelines 2020

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SECTION XIV

Ethical Cost–Benefit Relationship

The Ultimate Justification for Using Animals in Research

62

The Concept of Ethical Costs

- The use of laboratory animals as surrogates in research represents an ethical cost.
- The ethical cost increases when:
  - Animals higher on the phylogenetic scale (vertebrates vs. invertebrates are used
  - Experiments involve pain, discomfort or distress
  - The research requires more animals

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The Concept of Ethical Costs *Cont'd*

- The ethical cost decreases when:
  - Animals lower on the phylogenetic scale are used (invertebrates vs. vertebrates)
  - Experiments involve less (or no) pain, discomfort or distress
  - The research requires fewer animals

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IACUC Approval Criteria

- The ethical cost of using animals in research
  - (*position on the phylogenetic scale; anticipated adverse effects; number of animals used*)

is, in the non-empirical judgement of the IACUC:

- outweighed or balanced by the *potential* (*short and/or long term*) benefit of the research
  - (*improved human and/or animal well-being, provision of significant new knowledge, or contribution to the good of society*).

USGP II, PHS Policy, The Guide, p. 27, and a societal mandate

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EU Directive

"The likely harm to the animal should be balanced against the expected benefit of the project."

Directive 2010 (63) EU (39), 9/22/2010

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CIOMS-ICLAS IGP

- "…a system of animal use oversight … should promote a harm-benefit analysis … balancing the benefits derived from research … with the potential pain and/or distress experienced by the animal."

CIOMS-ICLAS IGP X (2012)

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The Guide - AAALAC

- "…the IACUC is expected to weigh the objectives of the study against potential animal welfare concerns"

The Guide, p. 27

- AAALAC International expects the IACUC (or comparable oversight body), as part of the review process, "will weigh the potential adverse effects of the study against the potential benefits that are likely to accrue as a result of the research … This analysis should be a primary consideration in a review process."

AAALAC FAQs on Harm/Benefit Analysis, 2021

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Conclusion

- The use of animals in research is a privilege, not a right.
- Society expects animal use to be justified, humane and ethical.
- Ethical research is characterized by 6Rs:
  - Replacement
  - Reduction
  - Refinement
  - Responsibility
  - Reproducibility
  - Respect
- The IACUC serves as society's gatekeeper.

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