

# The Three Rs of Animal Research: What they Mean for the Institutional Animal Care and Use Committee and Why

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**Abstract** The Institutional Animal Care and Use Committee (IACUC) is entrusted with assessing the ethics of proposed projects prior to approval of animal research. The role of the IACUC is detailed in legislation and binding rules, which are in turn inspired by the Three Rs: the principles of Replacement, Reduction, and Refinement. However, these principles are poorly defined. Although this provides the IACUC leeway in assessing a proposed project, it also affords little guidance. Our goal is to provide procedural and philosophical clarity to the IACUC without mandating a particular outcome. To do this, we analyze the underlying logic of the Three Rs and conclude that the Three Rs accord animals moral standing, though not necessarily “rights” in the philosophical sense. We suggest that the Rs are hierarchical, such that Replacement, which can totally eliminate harm, should be considered prior to Reduction, which decreases the number of animals harmed, with

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Refinement being considered last. We also identify the need for a hitherto implicit fourth R: Reject, which allows the IACUC to refuse permission for a project which does not promise sufficient benefit to offset the pain and distress likely to be caused by the proposed research.

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## Introduction

In our experience, most researchers are highly ethical individuals who deeply care about their work and study organisms. Animal research is nonetheless increasingly governed by legal regulations that identify minimal acceptable standards and procedures that must be followed. The specifics vary somewhat from country to country (see reviews and applications in various countries and animal models in, e.g., Mepham 2008, pp. 195–196; Perry et al. 2011; Russell 2013). As Mepham (2008, p. 196) points out, these regulations are informed by and strongly emphasize a set of principles called *the three Rs*, generally attributed to Russell and Burch (1959). These articulate the common sense, intuitive view that non-human animal experimentation should be morally permissible and as humane as possible.

“Among other requirements, research facilities ... must ... appoint an Institutional Animal Care and Use Committee (IACUC) ... which ... is required to perform certain functions in order to ensure the facility’s compliance with the AWA regulations. As one of these functions, the IACUC must review proposed activities involving animals that are performed at the facility...” (Federal Register, 9 CFR Parts 1 and 2, [Docket No. APHIS–2014–0050]). In the US, the IACUC must assign a proposed procedure to one of several USDA pain and distress categories, with justification and alleviation requirements commensurate with the extent of the harm expected. Where data about non-humans are lacking—as they often are—legislation in various countries explicitly requires the IACUC to use what is known about the effects of similar procedures on humans (Perry et al. 2011). Even experienced researchers may slip into the anthropomorphic assumption that what affects humans has similar effects on other animals, though something that affects us may have a different effect on another species, and something that harms that species may not affect us in the same way.

Though the laws in North America focus on pain and distress, the goal is clearly to reduce harm (in the sense of physical or perceptual damage, discussed in greater detail below) in general. Some authors (e.g., Stafleu et al. 1999) explicitly use the terminology of “harm” and “benefit” rather than “pain and distress” in discussing the calculus of IACUC decision-making.

Legally, funding agencies have relegated the job of identifying and addressing ethical concerns to IACUCs, just as they have relegated the job of identifying and addressing conservation concerns to agencies such as the US Fish and Wildlife Service. Instead, funding agencies focus on evaluating other aspects of proposed work. Moreover, many of the proposals submitted to the IACUC do not involve externally-funded research, and thus a significant proportion of studies being

evaluated have not even received external scrutiny. Although the existence, composition, and duties of the IACUC are mandated by law, ethical advice for addressing the complex dilemmas IACUCs face is in surprisingly short supply. Despite the presence of extensive written guidelines, the actual ethics involved in trading off benefits and costs of a study are not clearly identified, and each IACUC must struggle in making such decisions. Although some authors have welcomed this vagueness as crucial for allowing local decisions to reflect differences in community standards, others have decried this situation (e.g., Ferdowsian 2011) and attempted to provide more explicit, sometimes numerical guidance (e.g., Stafleu et al. 1999; Mepham 2008).

Although *applications* of the Three Rs have been much discussed, rather little *analysis* of them has appeared in print. We clarify the Three Rs by fleshing out the meanings of some key concepts, making some implicit principles explicit, and providing realistic examples. We address what may be the biggest lack of the Three Rs: they do not explain *why* researchers should try to minimize harm to animals, and we make explicit an important point which is not technically included within the Three Rs: some conceivable research is not ethical and should not go forward. Our goal is not to provide a prescriptive one-size-fits-all solution to the wide diversity of issues facing IACUCs. Providing philosophical clarity can hopefully prevent easily avoidable errors. However, it is impossible to provide clear-cut algorithms for resolving all borderline cases. We do not inject ourselves into discussions of what should happen outside the scientific research realm, nor do we explore the contentious issue of sentience and its additional implications. Rather, we seek to provide scientists and IACUC members with understandable, philosophically-sound analyses of the Three Rs and what they mean, and to suggest a thought process that might help analyze proposed projects and balance often conflicting benefits and harms so that an appropriate decision can be reached. As the IACUC must, by law, include non-scientists, we sometimes prefer to err on the side of belaboring a point that might be obvious to an experienced biologist. Finally, we do not claim that every part of our analysis is a departure from what some, many, or even all IACUCs currently practice. Indeed, some parts of the analysis represent common practice. Nonetheless, we believe that (a) some IACUCs may not currently be abiding by all the suggestions that follow, and (b) even those that do may benefit from a clearer explication of why that might be a good idea, if only for use in training new members.

## The Three Rs

Researchers have a moral duty to avoid inflicting unjustified suffering, the fundamental principle being:

- (1) Research that harms animals less is morally preferable to research that harms animals more, other things being equal.

The “other things being equal” clause is very important. For example, it implicitly includes the notion that the knowledge gained must be the same, or equivalent in value.

Russell and Burch (1959, p. 64) aimed to help researchers minimize harm to animals by identifying three general ways to modify an initial research plan (emphases ours):

“**Replacement** means the substitution for conscious living higher animals of insentient material. **Reduction** means reduction in the numbers of animals used to obtain information of a given amount and precision. **Refinement** means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used.”

There are two other well-known “Three Rs.” One, from the realm of education, is a-hierarchical: *reading, writing, and ‘rithmetic* are instilled simultaneously. The other set, from the realm of sustainability, is different in that one should first try to *reduce* the use of resources, then *reuse* what has been used, and only then *recycle* what is left. Although recycling is desirable, it is subordinate to the need to minimize the use of resources to begin with. In many cases, IACUCs view applications holistically, considering multiple issues more-or-less simultaneously and treating the Three Rs as similar to the educational ones. We argue that the Three Rs of animal ethics should normally be considered hierarchical, like the Three Rs of sustainability, and animal researchers should usually begin their ethical consideration by asking whether they can acquire the same (or equivalent) knowledge without harming animals. After all, if the desired outcome can be achieved with no harm whatsoever, the task of the IACUC is straightforward. Only if harm cannot be avoided must reduction be considered, and only when the number of animals used has been minimized does it make sense to further refine the methods so as to minimize the pain and suffering inflicted upon those animals that must be harmed.

The general approach of harming as few animals as possible and as little as necessary is endorsed by almost all parties and is enshrined in law in the United States (Animal Welfare Act 2000; Ibrahim 2006; National Institutes of Health 2002; National Academy of Sciences 1996) and elsewhere. Some animal rights philosophers take the need to protect animals further and call for the complete abolition of animal experimentation, claiming that *any* use of animals is immoral (Cohen and Regan 2001; Bernstein 2004; Francione 2008). For example, Linzey and Linzey (2015) recently approvingly cited Peattie (1984), who stated that “The deliberate and routine abuse of innocent, sentient animals involving harm, pain, suffering, stressful confinement, manipulation, trade, and death should be unthinkable.” However, the three Rs represent an anthropocentric set of principles that clearly subordinate animal interests to human ones and do not question the morality of using animals as means to satisfy human ends (for several perspectives on this issue see Beauchamp and Frey 2011; Monamy 2009). Arguing for or against that position is beyond the scope of this paper. We accept the assumption that there are morally better (or less bad) ways of using animals (Singer 1990; Bekoff 2007; Palmer 2010), and argue that the Three Rs can guide researchers towards these. Moreover, as Stafleu et al. (1999) note, the common interpretation of the Three Rs suggests that some uses provide greater benefits, and thus greater harm can be allowed. This is the approach we adopt in this paper.

Our restatement of the Three Rs is the following:

- *Replacement*: Researchers should try to eliminate harm by *replacing* the animals targeted with entities that cannot be harmed (e.g., computer models, tissue cultures), or with animals of other species that would be harmed less.
- *Reduction*: Researchers should decrease harm to animals by *reducing* the number of individual animals targeted by the research plan.
- *Refinement*: Researchers should decrease harm to animals by *refining* or modifying their methodology to inflict less harm on each targeted animal.

In addition, research plans that might gain significant knowledge should not be implemented if the cost in animal suffering is “unacceptably high.” Moreover, if a research plan has little chance of gaining significant knowledge, then even minimal harm to animals is unjustified. Of course, few proposed studies are truly futile, and the task facing the IACUC in determining whether the benefits justify the harms is thus rarely trivial. To emphasize these points, we enjoin a fourth R:

- *Refusal*: Researchers should decrease harm to animals by *refusing* to proceed with research if the knowledge gained would not justify the harm to animals.

This may require the IACUC to do something it is typically loath to do: evaluate the quality of the science involved in the proposed project in order to identify not just the stated goals but also the likelihood of achieving them (Staffeu et al. 1999).

## Harm

Below, we offer a common-sense (Lemos 1986; Rawls 1971) clarification of the crucial concept of “harm to animals”, which remains surprisingly controversial (Degrazia and Rowan 1991). The absence of a clear standard of harm makes it tempting to specify harm to animals in ways convenient or intuitive for the researcher or legislator. Even obvious harms and interconnections are difficult to recognize when they run contrary to expectations.

- a. Anything can be “harmed”: microbes can be killed and mountains can be leveled. Although pleasure and pain are not the only sorts of harms, the Three Rs define “harming” as impeding the well-being or interests of an animal capable of experiencing pleasure and pain. “Which animals feel pleasure and pain?” is a much discussed question that is beyond the scope of this paper (Nuffield Council 2005; Bekoff 2007; ILAR 2009).
- b. Increasing an animal’s overall pain or decreasing its overall pleasure is harmful. Inflicting more pain is more harmful than inflicting less pain, other things being equal.
- c. Pain and pleasure can be psychological or physical, future as well as present, etc. Thus, for example, inducing fear is harmful, even though the harm is “only” psychological.
- d. Some pains and pleasures are commensurable, but others are not. Physical and emotional pain cannot be put onto the same scale, for example.

- e. Pain is not the only sort of harm. Although some disagree (e.g., Regan 2001; Singer 1990; Frey 1980), common sense says that killing an animal is harmful because life is of fundamental value to it. It follows that killing an older or short-lived animal is less harmful than killing a younger or longer-lived animal, other things being equal, because it minimizes life-years lost.
- f. Because some harms block others, inflicting a certain harm upon an animal may be less harmful than the alternatives. For example, euthanizing a suffering animal may be less harmful to it, on balance, than doing nothing—and is required by law in many cases. To borrow a concept from biomedical ethics, the Three Rs aim to minimize Quality Adjusted Life Years lost because of research.

A research plan is harmful to animals if and only if it makes things worse for them. But comparison of the pre- and post-research situations of the animal subjects is tricky. We offer a few guidelines:

- a. Research may benefit as well as harm a single animal, so research plans must be compared with respect to overall, rather than momentary harm to individual animals. For example, administering a vaccine may be frightening and physically painful, yet be beneficial overall. The fact that an animal struggles to avoid a vaccination does not imply that the procedure is overall harmful.
- b. Research may benefit as well as harm more than one animal, so research plans must be compared with respect to overall net, rather than gross harm across all animals involved. For example, prolonging the lives of some animals through vaccination may lead to overpopulation and result in mass starvation. The commitment to minimizing harm includes the commitment to sacrificing the interests of the few for the sake of the many, as the Reduction criterion makes clear.
- c. Harms and benefits are often synergistic, so the presence of one sort of harm or benefit in an animal may enhance or detract from another. Fear may increase the physical pain of an injection, for example, and physical pain may cause fear.

## Moral Duty

One research plan might be preferable to another for many reasons. Research that is less costly is preferable to more costly research, other things being equal. But the Three Rs are not saying that we should minimize animal harm for economic or aesthetic reasons. Although it has not previously been made explicit, the “should” in the Three Rs clearly expresses a *moral* obligation.

But why is minimizing harm to animals the morally right thing for researchers to do? The Three Rs implicitly state that researchers have a moral duty to minimize harm to animals out of respect for the interests of the animals, which must be considered and may at times outweigh some interests of humans. This view is very much consistent with the assessment of Linzey and Linzey (2015) that “individual animals have worth in themselves” and that, therefore, “causing harm to individual

sentient beings ... minimally requires strong moral justification.” Like Mepham (2008, p. 385), we consider proper treatment of research subjects an integral part of the ethical standards expected of scientists in the biological disciplines. It may surprise some researchers (and animal rights advocates) that the Three Rs accord animals moral standing, though not necessarily “rights” in the philosophical sense. It is important not to overstate this conclusion, which says nothing about the basis or extent of the moral significance of animals. Nonetheless, the Three Rs clearly state that it is greater than zero, a view that is in agreement with the statement by Linzey and Linzey (2015) that “Ethical research techniques need to be fully institutionalized,” but clearly not with their conclusion that animal research “needs to be de-normalised and de-institutionalised”.

## Knowledge

That knowledge gained is a good thing is axiomatic to scientists, but it is also a morally relevant good because it has the potential to benefit others. Like “harm to animals,” the meaning of “knowledge” is vague and discipline-specific. Consider the following three questions:

1. *What counts as knowledge?* Replicating an experiment with a larger sample size is sometimes viewed as production of new knowledge, but often treated as redundant or less valuable than the initial work. Since replication is essential for verification, and therefore a crucial part of the scientific method, none of our claims privilege new research over confirmatory research.
2. *How are different bits of knowledge to be compared?* It is sometimes quite difficult to say whether one bit constitutes more knowledge, or is more valuable than another bit. Such valuation must be performed in order to compare research plans, yet different disciplinary frameworks provide different answers.
3. *How are the bits of knowledge interconnected?* Not only bits of knowledge, but also new insights about the interconnections among them count as knowledge. Researchers must try to understand the relationship among the bits of knowledge in order to evaluate the worth of any individual bit. Discipline-specific answers will be needed that are beyond the scope of this paper.

## An Example

To illustrate our views we present a case study and discuss it from the perspectives of each of the Rs.

For several centuries, natural history collections have been, and still remain, essential in biological research (e.g., Suarez and Tsutsui 2004). Originally used primarily for systematic, morphological, and biogeographic studies, they have in recent years offered growing value to studies of ecology, epidemiology, conservation, and especially the effects of anthropogenic climate change (Suarez and

Tsutsui 2004; Pyke and Ehrlich 2010; Johnson et al. 2011). Although the ideas embodied by the three Rs are not new to the museum world (Coleman 1927), they have not often been a major component of the collection planning process (Vucetich and Nelson 2007). Accusations that collection of animals for zoological research are cruel and unethical also go back more than two centuries (Hollerbach 1996).

Our scenario, loosely based on applications to actual IACUCs, involves Dr. Bruce, a well-regarded investigator who has a joint appointment as Director of the Gotham University Natural History Museum and a professor at the institution's College of Life Sciences. Dr. Bruce requests IACUC approval for a protocol that allows the collection of unlimited numbers of individuals of any mammal species at any location. Although this may seem like an unlikely scenario, we have been informed by colleagues who serve on IACUCs at major universities that such requests are, indeed, still sometimes submitted for various taxonomic groups. What should the Gotham University IACUC do? Neither the law nor the American Society of Mammalogists (ASM 2011) resolve this question.

## Replacement

The first derivative of principle (1) is this:

- (2) Research that does not harm animals is morally preferable to research that harms animals, other things being equal.

This principle is straightforwardly applied in certain laboratory studies, where computer models or tissues can provide just as much insight as working on animals. Using such stand-ins is unlikely to be a possibility for most field ecological studies, however, and has limited utility in other situations as well. Can it be relevant to Dr. Bruce's work?

When one cannot devise fruitful and fully harmless research plans, the first R calls for replacing the target animals with ones which will be harmed less. For example, researchers could draw blood from healthy animals which will have no trouble replenishing it, rather than injured or otherwise compromised animals which are likely to suffer from the procedure. A more common interpretation of this rule is that harm can sometimes be decreased by replacing one study species with another species. Many authors suggest that sentience is key in deciding which organisms to avoid when possible, and most, including the law in many countries, identify most or all vertebrates as particularly deserving of protection. Yet there remains disagreement about what characteristics are key: higher priority animals may be those that reason; have autonomy; have language; use tools; express sympathy and other pro-social emotions; are self-aware; are subjects of a life; are "charismatic mega-fauna;" are vertebrates; and more. Many of these rating schemes are anthropomorphizations that privilege certain characteristics and practices simply because they are typical of humans (e.g., Bekoff 2010), but they sometimes yield different rankings. For example, octopi are lower priority animals by some measures because they are invertebrates, yet higher priority according to other views because they can use tools and solve puzzles.



Although the three Rs are anthropocentric, they are not anthropomorphic and do not ask us to understand animals in human terms. We suggest that the distinction between deserving greater or lesser consideration, in terms of harms, should also be made non-anthropomorphically, avoiding criticisms such as those by Bekoff (2010). Rather, the distinction should arise straightforwardly from commonsense claims about animal harm plus principle (2), above. We define a *complex experience* as one in which several sorts of pain and/or pleasure occur simultaneously. Clearly, a complex experience consisting of multiple pleasures is more pleasurable than a simple experience consisting of only one of these pleasures, other things being equal. Consequently, if an injection will cause turtles to feel only physical pain, but will cause monkeys to feel both a similar physical pain and also emotional pain (fear, anger, etc.), then administering the injection to a turtle causes less harm than administering it to a monkey. One animal is identified as deserving greater consideration than another if and only if it has more complex experiences, and is capable of more complex pleasures and pains. This definition is similar to that of Singer (1980), although his is based upon preference satisfaction rather than desire. Thus:

- (3) Research which deprives animals of simple pleasures or inflicts simple pains is morally preferable to research which deprives animals of complex pleasures or inflicts complex pains, other things being equal.

Using this criterion to exhaustively specify which animals deserve greater consideration is a daunting task. If animal A feels two pains for animal B's one, then harming B twice for every harm inflicted on A might seem to be an even exchange. Unfortunately, different sorts of harms are incommensurable. We cannot say whether 2 s of mild physical pain plus fear is more or less harmful than 4 s of intense physical pain without fear. Similarly, except in extreme cases, we cannot say whether it would be better to inflict extended periods of intense pain to members of a lower priority species or short bursts of mild pain to members of a higher priority species. Legally, USDA pain and distress categories to some extent address these issues by requiring more substantial justification for procedures perceived to be more harmful. Nonetheless:

- (4) Research which harms lower priority animals is morally preferable to research which harms higher priority animals, other things being equal.

How does this apply to our hypothetical scenario? Dr. Bruce is a mammologist, so this kind of replacement is not an option. This is not the case for many lab-based studies, but cases where a particular kind of organism is especially suited to the study being planned are not uncommon. Nonetheless, Dr. Bruce can perhaps shift his research from elephants to mice, for example. In reality, much collecting is done in preparation for unspecified future studies, rather than for a current research project (e.g., Bebbler et al. 2010). Since the exact future use of Dr. Bruce's collection is unknown, it is very hard to judge what kind of specimen or record might provide the ideal source of knowledge. The IACUC would presumably seek some clarifications from Dr. Bruce regarding intended future uses. Depending upon what Dr. Bruce says, the IACUC might require the replacement of whole animals with accessioning of photographic evidence (recognizing that the mere presence of

researchers might cause distress) or of non-invasively obtained DNA samples (e.g., Beja-Pereira et al. 2009), though these methods do not meet all needs. In the case of many of the studies which might be conducted on the museum specimens, however, replacement will be impossible. The IACUC may find itself in the uncomfortable position of approving or denying the request based on information which is, by definition, partial.

## Reduction

The second R enjoins researchers to ask whether, having failed to replace their study organisms with lower ones, they could acquire the knowledge they seek in ways which harm fewer animals of the same sort. The common sense principle underlying this question is:

- (5) Research that harms fewer animals is morally preferable to research that harms more animals, other things being equal.

Principle (5) highlights a trade-off between knowledge-gained and number-of-animals-harmed. Obviously, when knowledge-gained is constant, the fewer suffering animals the better, and when harm to animals is constant, the more knowledge-gained the better [see principle (11) below]. When research plans involve different sorts of animals or different sorts of harm, other things are not equal.

When the parameters of a study are well-known, a power analysis is often used to calculate the minimal number of animals likely to produce a defensible result. This is rarely the case for field studies, however. How should trade-offs between gaining knowledge and reducing harm to animals be adjudicated in this situation? Common sense suggests that each value outweighs the other at one extreme. Thus:

- (6) If one research plan harms animals only a bit more than another, and yields much more knowledge, then it is morally preferable, other things being equal.
- (7) If one research plan yields only a bit less knowledge and harms animals much less, then it is morally preferable, other things being equal.

Animal welfare and animal rights theorists maintain that animals have value in themselves; they have very high moral standing; their interests are intrinsically valuable (Regan 1983, 2001; Franklin 2005; Singer 1990) and thus animal welfare will almost always take priority over knowledge-gained (e.g., Linzey and Linzey 2015). Principles (6) and (7) incorporate the core claim of Singer and Regan: Animals' interests merit some consideration, thus animal welfare is morally significant. However, principle (6) allows researchers to violate what Regan would consider the rights of animals and privileges the interests of humans over the interests of animals, contrary to Singer's view.

Extreme anthropocentrists maintain that animals are valuable only insofar as they are useful to people. They lack moral standing (Cohen and Regan 2001; Monamy 2009; Frey 1980) and thus knowledge-gained almost always takes priority. Principles (6) and (7) also incorporate the core claims of Frey: Animals' interests and people's interests do not merit equal consideration, and people come first.

However, principle (7) is incompatible with Cohen and Frey's views, requiring researchers to refrain from pursuing minor knowledge gains in order to spare animals from major harm.

What about cases where one research plan will provide much more knowledge at the cost of much more animal harm? Or a bit more knowledge at the cost of a bit more animal harm? At first glance, it is tempting to think that one must be morally better than the other and that research ethics should provide a method for identifying the best option. However, in many situations there is no morally best option because different options produce incommensurable goods and harms. Luckily, sophisticated moral theories (consequentialism, deontology, virtue ethics, and common sense morality) do not demand that we take the best option in a situation, but rather that we take any one of the acceptable options (Ferry 2013; Hill 1992; Hursthouse 1999; Slote 1984). The crucial thing is to identify and reject the immoral options. Thus,

- (8) If research plan A is likely to harm moderately more animals than research plan B but also likely to yield moderately more knowledge than plan B, then neither plan is morally preferable to the other, other things being equal.

What is important is to settle on one of the acceptable solutions, rather than to seek a (possibly non-existent) "best" solution.

To the extent that Dr. Bruce conducts his collections humanely, and immediately and painlessly euthanizes animals, no suffering is caused and the law in many countries sees no harm to animals. Nonetheless, our hypothetical IACUC is likely to consider that an approved protocol for collecting any number of any species at any location (rather than, say, 5 individuals from each of a set of identified species at each of a set of named locations) holds the potential for great abuse of the Reduction principle. Indiscriminant collecting, however humane, would constitute "harm" and be unethical.

A reasonable IACUC might ask Dr. Bruce to provide specific goals and clear guidelines for minimizing the number of animals to be used. Dr. Bruce might object that the goal is to create a baseline for future comparative research whose nature may not even be knowable at this point, and which might depend on equipment that does not currently exist. However, this justification is too broad, since it could hypothetically allow all individuals of the species to be collected. Moreover, the unknown future method might require methods of preservation not currently in use, making specimens collected today useless for that purpose. One IACUC, primarily motivated by the value of potential knowledge, might approve a very broad collection protocol. Another, mostly concerned about the loss of life or ecosystem impacts of over-collecting, might greatly limit approved collections. Neither IACUC is necessarily wrong: both options are morally justifiable.

## **Refinement**

Having addressed the two previous Rs, common sense and the third R demand that researchers ask themselves whether they can acquire the knowledge they seek in a way which causes less harm to the same individual animals, or which renders harm

to these animals less likely. Common practice is to choose procedures which cause less harm and euthanize an animal injured unintentionally during a study, rather than allowing prolonged suffering. The underlying principles are:

- (9) Research which harms individual animals less is morally preferable to research that harms the same animals more, other things being equal.
- (10) Research which has a lower probability of harming animals is morally preferable to research that has a higher probability of harming the same animals, other things being equal.

But how is one to compare degree-of-harm [principle (9)] and likelihood-of-harm [principle (10)] when designing a project? How are trade-offs among these and the previously discussed issues to be made? Other things being equal, is research that harms fewer animals to a greater degree morally preferable to research that harms more animals to a lesser degree? One practical example of this relates to animals involved in studies in which they undergo surgery and are allowed to recover. Law in the US requires that all animals undergoing “survival surgery” be euthanized afterwards, regardless of their actual health. This reduces individual lifetime pain, but increases the number of animals harmed because the same individuals cannot be used in other studies for which they would otherwise be appropriate. As before, none of these conflicts can be resolved a priori. None of these values universally trumps the others. Rather, each outweighs the others at extremes but multiple solutions are ethically acceptable in ordinary situations.

Another important question, only infrequently asked, is whether modifying the research design can produce more knowledge without increasing the amount of harm. Thus,

- (11) Research which gains more knowledge is morally preferable to research which gains less knowledge, other things being equal.

The imperative underlying principles (5) and (11) is the same: maximize knowledge-gained per bit of animal-harm. If animals must suffer or die for the sake of knowledge, then their suffering or death should be as fruitful as possible. Researchers should not only minimize animal harm, they should also squeeze as much knowledge as possible out of each bit of unavoidable animal harm. Refining a protocol to make sure that the maximum amount of information is derived from the work could take the IACUC into new territory, however.

Because the protocol submitted by Dr. Bruce is so open-ended, the task faced by the IACUC is especially difficult. Possible tradeoffs between various kinds of harm and knowledge gained abound. Given diverse values placed on costs and benefits associated with any particular design, different IACUCs might legitimately reach divergent conclusions about what is acceptable. The methods used by Dr. Bruce to obtain specimens may certainly be amenable to refinement. For example, Powell and Proulx (2003) and Iossa et al. (2007) contend that there is room for improvement in the methods currently used in such studies. The challenge for the IACUC, especially at a small institution, is to assemble sufficient expertise to assess the claims made by the researcher, perhaps by asking colleagues outside of the IACUC, and maybe even outside of Gotham University, to provide an evaluation.

To maximize utility the IACUC might require Dr. Bruce to provide metadata for collected specimens that may not have otherwise been collected, in order to increase the value of specimens for future workers. It might go a step further and require that collections also include non-native species that are of no interest to Dr. Bruce, but that will have future value for studies of invasive species and their ecological consequences (Suarez and Tsutsui 2004). A commitment that specimens collected under a particular protocol will be available to other researchers, will be deposited and accessioned at a recognized museum within a realistic time frame, that their data will be digitized and made available on-line or within discipline-specific databases (Drew 2011), could also be required. A mandate that publications based on the collections appear within a reasonable amount of time, in cases of collections aimed at a specific study, could be added as well. The IACUC could even require increased coordination with other museums to reduce redundancy (consistent with the Reduce rule) and increase geographic, temporal, and taxonomic coverage, thus increasing possible future value, as called for by Johnson et al. (2011) and Ward (2012). Many researchers will doubtlessly chafe at such additional requirements, and many IACUCs will be wary of the need to monitor compliance with such requirements long after the protocol expires.

## A New R: Refusal

The Three Rs of Russell and Burch (1959) are injunctions for minimizing harm and maximizing knowledge in the course of research. They are phrased in a way that implicitly assumes that all research will be permitted to go forward, although some research plans might require tweaking. But this ignores the possibility that some research should not be performed at all.

Great discoveries are occasionally accidental and promising lines of research do not always pan out, but some research plans are so badly conceived that they almost surely produce no benefit and harm animals in the process. Common sense says that such studies should not be allowed to proceed. But while committees have been able to request clarifications and delay, their mandate does not actually allow them to outright reject a proposal on those grounds. We therefore enjoin a final question and a fourth R: Does the research plan have a reasonable chance of yielding knowledge, or is it just a waste of animal harm? Thus,

- (12) Research which would yield gains in knowledge which are not worth the harm caused to animals, should not be pursued.

Principle (12) is a minimally constraining principle which comes into play only when no amount of tweaking will yield a fruitful plan. Principle (12) is similar to principle (7) but goes beyond it in making explicit the following qualification of all of the previous principles: one plan may be morally preferable to another, yet neither plan may be morally acceptable because both may fail to meet the Refusal criterion. There are some clear cases of unjustifiable research. For example, the claim has repeatedly been made, most recently by Linzey and Linzey (2015) that “we now know that many experiments have provided misleading or erroneous

results.” Such claims are, of course, strongly denied by many researchers (see, e.g., review in Mukerjee 1997), but others agree that basic assumptions underlying the usefulness of some animal research remain poorly substantiated (e.g., Horrobin 2003; Greek and Greek 2010; Shanks et al. 2009).

As an example of a project that should be rejected, suppose the project proposed by Dr. Bruce requires the killing of 100 black-footed ferrets—roughly the entire remaining population of this highly endangered species—just because having them in a museum might be helpful to some future, unspecified study. That Dr. Bruce could not possibly get the necessary collection and transportation permits associated with such an overly broad project would not absolve the Gotham University IACUC from its ethical responsibility to refuse permission, something that neither the Three Rs nor current regulations allow it to do.

The example above is quite simplistic, intended to show the conceptual need for a Rejection principle rather than provide practical guidance on how such a principle is to be implemented under a more realistic scenario. As we have stated elsewhere, a single, simple method of determination is neither possible nor desirable, since different IACUCs will evaluate the “harm to animals” and “knowledge” associated with a given project in somewhat different ways. We believe it is important to maintain their flexibility in addressing such complex issues, so long as the chosen solution lies within the realm of those that are morally acceptable under the guidelines above. We note that bans on the use of great apes in invasive research, enacted by the regulatory agencies in multiple countries (Knight 2008), represent a form of the Rejection principle in that they offer a blank statement that no amount of knowledge gain could justify the animal harm involved in such work.

## Conclusion

We suspect that the broad appeal of the Russell and Burch’s (1959) Three Rs rests not only on their plausibility, but also on their vagueness. The ambiguity of the terms in which they are couched allows people with diverse views to endorse their own interpretations without deliberating with others upon their meaning or foundations. Although this state of affairs has its advantages, this paper aims to help researchers and IACUCs more thoroughly understand what they are endorsing and why.

Our analysis begins with the common-sense generalization that research that harms animals less is morally preferable, and ends with the novel conclusion that proposed research which would yield gains in knowledge which are not worth the harm caused to animals should be rejected by the IACUC. We employ a non-anthropocentric definition to justify giving some animals greater consideration over others in research without anthropomorphization. We also reveal that the Three Rs accord animals moral standing, something both researchers and those opposing research may find surprising. We suggest that IACUCs may require researchers to conduct additional work that enhances the value of proposed research, so long as such obligations are not too onerous. Finally, we add a fourth R to capture an important aspect that is implied, but not previously explicitly included within the Three Rs: the ability to reject proposed research, something not currently allowed.

These Four Rs do not resolve all borderline cases or guide every difficult decision to a straightforward solution, nor do we try to balance the moral claims of animals against the claims of ecosystems, species, populations, etc. (but see Curzer et al. 2013a). However, the Rs do have two important uses. First, they clarify and codify some ways to think about moral conflict cases. Second, they constitute boundary constraints beyond which it would be unethical to venture. The addition of the fourth R does not dramatically change the character of the principles, but it does change their rhetorical force. The fourth R makes it clearer that animals have moral standing and may not be harmed without a good reason.

In recent decades, philosophical and legal views of animal research have been shifting, with greater attention being paid to animal welfare (Mukerjee 1997). In this and other papers, we and others have attempted to reconcile the need for research that involves animals with a desire to maximally protect individuals, populations, species, and ecosystems from harm (e.g., Curzer et al. 2013a,b; Perry et al. 2011; Perry and Perry 2008a,b). However, changes have been somewhat one-sided, and we find it discouraging that the animal protection literature shows relatively little sign of greater nuance in the views expressed. We very much hope that the conversation will increasingly involve greater understanding and accommodation on both sides of this ongoing philosophical and practical debate.

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