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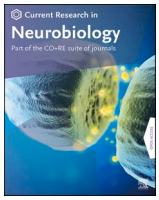

A framework and resource for global collaboration in non-human primate neuroscience

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ABSTRACT

As science and technology evolve, there is an increasing need for promotion of international scientific exchange. Collaborations, while offering substantial opportunities for scientists and benefit to society, also present challenges for those working with animal models, such as non-human primates (NHPs). Diversity in regulation of animal research is sometimes mistaken for the absence of common international welfare standards. Here, the ethical and regulatory protocols for 13 countries that have guidelines in place for biomedical research involving NHPs were assessed with a focus on neuroscience. Review of the variability and similarity in trans-national NHP welfare regulations extended to countries in Asia, Europe and North America. A tabulated resource was established to advance solution-oriented discussions and scientific collaborations across borders. Our aim is to better inform the public and other stakeholders. Through cooperative efforts to identify and analyze information with reference to evidence-based discussion, the proposed key ingredients may help to shape and support a more informed, open framework. This framework and resource can be expanded further for biomedical research in other countries.

1. Introduction

More than ever, scientists across the world understand the societal benefits and importance of enabling and promoting responsible research. Scientific research and advances often require international working groups, subject to operating within different regulatory frameworks governed by the ethical, welfare and regulatory standards in each country. There is a pressing need for frameworks and resources to support international collaboration, which are sensitive to societal and governmental regulation and legislation (Abbott, 2014; Bayne et al., 2015; Bayne and Turner, 2019; MacArthur Clark and Sun, 2020). For scientific breakthroughs and advances that depend on international working groups, it is essential that scientists and other stakeholders are empowered with information and guidelines that can support collaboration across the world (Adams, 2013). Here, we consider the regulations of non-human primate (NHP) neuroscience research across three continents and propose key ingredients that can help to foster international synergy.

Today's notion of '*team science*' refers to relatively new formats that bring together diversity, complementary expertise, resources, data, specialist equipment and/or techniques (Hall et al., 2018; Ledford, 2015). Added value occurs when scientists can work seamlessly across borders (Guerrero Bote et al., 2013) to share resources and intellectual insights, shortening timeframes for discoveries and increasing sample sizes through collaborative scientific work. However, despite the great potential of team science, the pragmatics and local diversity in regulations can be difficult to navigate, thereby, precluding efficient collaborations. Further, when scientific objectives include animal models, collaborative efforts require an informed and shared understanding of animal welfare and ethical approaches in the country in which the research is conducted. Perceived or real differences in animal research regulations across countries may hinder global collaboration and what can be achieved scientifically. For example, if two researchers from different countries are interested in collaborating, the two respective local animal care committees overseeing the experiments pursued by the two researchers normally request detailed information on the regulations on animal care in the collaborator's institution. More often than not, approving such a collaboration is subject to the collaborator's institutional policies being of standards as high as those held by the local institution.

A framework and information resource, such as the one developed here for NHP neuroscience, is relevant for all types of science dependent on animal research. Such resources may also inform intellectual contributions to support neuroscientific exchange with researchers in countries not conducting animal research involving NHPs.

NHP neuroscience research is strictly regulated around the world and work with NHPs requires appropriate species-specific knowledge and individual animal oriented expert care and specialized training Jain et al. (in press). Neuroscience research involving NHP animal models contributes to advances in scientific knowledge in relation to higher-order cognitive processes, sensory and motor systems neuroscience, and neuropsychiatric diseases and disorders (Buffalo et al., 2019; Klein et al., 2016; Klink et al., 2021; Lear et al., 2022; Maunsell and Treue, 2006; Mendoza et al., 2016). NHP research also contributes to the development of better care and treatments for neurological patients as well as those in other fields of medicine (Buffalo et al., 2019; Deere et al., 2021; Dijkman et al., 2019; Donahoe et al., 2009; Friedman et al., 2017; Jensen et al., 2020; Janssen et al., 2023). It is imperative that researchers, institutions, funders, regulators, policy makers, and the public are empowered to understand not only the continued need for neuroscience research involving NHPs and its societal value, but also the rigorous regulations and policies that govern this research across the globe.

In a recent paper, Mitchell et al. (2021) discussed the merits of future international collaboration involving NHPs that are based on shared and mutually agreed-upon principles. They also addressed the point of shared standards, highlighting that for global collaborations to function, we should be able to find common ground and utilize evidence-based approaches, wherever possible, to advance both science and animal welfare. Their article encouraged colleagues around the world, some of whom are involved in global collaboration, to consider the factors that contribute to or challenge the success of collaborative research involving NHPs. Some of these perspectives are shared in the articles of this special issue (Janssen et al., 2023; Procyk and Meunier, 2022), while others are presented elsewhere as a strategic plan to help coordinate the primate neuroscience community across the globe (e.g. the PRIMatE Data Resource Exchange, PRIME-DRE; Milham et al., 2020, 2022).

Here we compiled sources related to specific ethical considerations and welfare regulations pertaining to biomedical (neuroscientific) research with NHPs in multiple countries worldwide. We also propose key ingredients to build a collaborative framework that can offer solutions and information to support global collaboration in research involving NHP models, considering the variability in local, national, and international regulation. This resource initially focuses on macaques and marmosets, as the more common laboratory NHP models. For 13 countries national information is aggregated into a tabulated resource and maintained online (see PRIMatE Resource Exchange, https://prime-re.github.io/; Messinger et al., 2021). This resource is intended to be regularly updated by the research community to reflect changes in animal research regulation. This resource is not intended to be a comprehensive repository of regulatory or legislative documents. Rather, it represents a starting point for researchers, institutions, funders, policy makers, and the public to obtain basic information that can inform international collaboration. The resource itself is not stand-alone, but is integrated within a framework that provides guidance on the key ingredients supporting collaborative research with NHPs.

1.1. International resource on non-human primate neuroscience regulation

One major aim of this paper is the aggregation and sharing of animal welfare and regulatory guidelines. A comparative assessment of current national regulations is depicted in Fig. 1. This information is summarized in Tables 1 and 2. For an online version of the tables that will be updated visit: https://prime-re.github.io/hardware_and_protocols/global_collab.html).

One consideration to note when examining these individual nations' regulations is that although many European countries are bound to the EU Directive 2010/63/EU or, in North America, follow the guidelines set by the United States of America (USA) Office of Laboratory Animal Welfare (OLAW; the enforcing body for the federal research agency, National Institutes of Health (NIH); https://olaw.nih.gov/resources/tutorial/iacuc.htm), there is not yet a single set of ethical and regulatory standards. Agreed upon ethical and regulatory standards ensure that international collaborations can flourish (Mitchell et al., 2021). Guidelines that could be used as an international common standard, applicable to other nations, may be available in the form of a general animal welfare declaration (Petkov et al., 2022).

The first similarity to observe is that all countries included in this overview of guidelines have a local committee (LC) for animal welfare and ethical review, responsible for approving submitted NHP research applications (see Table 1 Section A). Each LC is typically composed of members with specific and relevant expertise, including veterinarians, other animal research scientists, statisticians, animal care technicians, medical doctors, legal and ethics experts, and persons who are not professionally involved in animal research or the institution performing the research. The LC can be formed at the institutional level or at the local governmental or provincial level. For example, in the USA, each research institution has its own LC called an *Institutional Animal Care and Use Committee* (IACUC) that reviews and decides on the approval of applications from research teams in their institution. A similar disposition exists in Belgium, Canada, China, Japan, Mexico, and Russia. In Germany, while each institution has Animal Welfare Officers to counsel researchers and ensure ethical conduct, research applications are reviewed and must be approved by regional governmental ethics committees (i.e., *Regierungspräsidium;* see TierSchVersV, §8, §9). Such LCs are responsible for the approval and regulation of research applications and for overseeing other animal welfare issues throughout their regional jurisdiction.

Both the institutional and regional governmental LCs strictly follow the national, and often also international, research animal welfare regulations in their evaluations and approval or rejection of research applications. However, review and approval at the national level, after approval by the LC, is also required in some other countries (i.e., France, India, Iran, the Netherlands, and the United Kingdom (UK)). A national committee for animal welfare review is represented by scientists and technicians with expertise in animal research and/or non-scientific members who are issuing the final approval, based on national guidelines, and recommendations by the LC (Table 1 Section B). An example of this two-step review process is outlined in the UK Guidance on Research and Testing Using Animals (UK Home Office, www.gov.uk/guidance/research-and-testing-using-animals), where the final approval of any NHP application is made by the UK Government Secretary of State for the Home Department, in accordance with the Animals (Scientific Procedures) Act 1986 in England, Scotland and Wales and the EU Directive 2010/63/EU (on the Protection of Animals Used for Scientific Purposes). Ongoing compliance in the UK for conducting regulated scientific procedures on NHPs is provided by the Animals in Science Regulation Unit (ASRU; see Table 1 Section A). Finally, in some other countries (i.e., Belgium, Canada and Mexico), the role of a national committee is to set the policies for the use of NHPs in institutions, and verify compliance with the policies by site visits/inspections of the institutions instead of contributing to the review and approval of individual NHP protocols.

Fig. 1A illustrates the use of local and national review processes in the 13 countries surveyed here, with each country conducting biomedical (neuroscientific) research involving NHP animal models. Taking together different ethical aspects in NHP research, Fig. 1B provides a picture of the common ground and overlap in the ethical and regulatory review for NHP neuroscience research and welfare standards.

1.2. Framework for international NHP neuroscience collaboration

Frameworks for global collaboration in scientific research ideally should include openly shared information pertaining to the scientific process and the principles that guide ethical and welfare regulations in different countries. A collaborative global welfare regulatory framework for NHP neuroscience research in this context should be robust, efficient, ethically grounded and evidence-based. First, we offer an international overview of national ethical and legal regulations of NHP neuroscience research based on our survey and review of present country regulations.

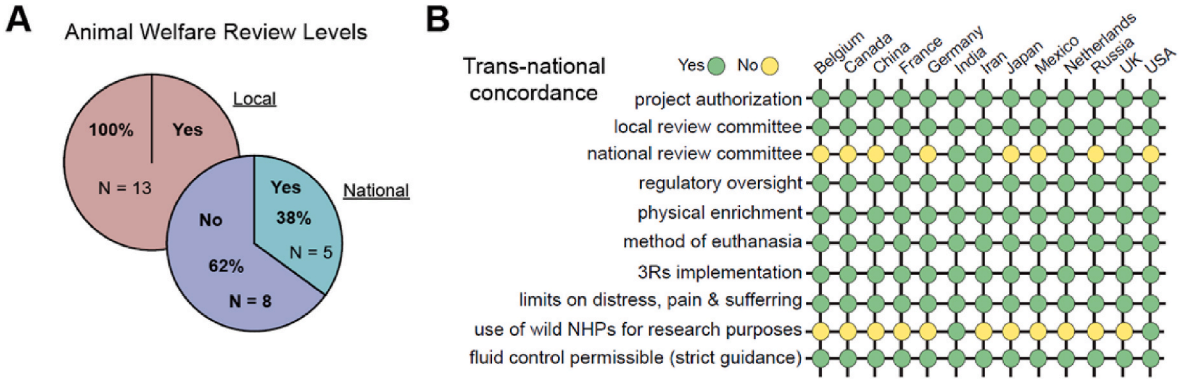

Fig. 1. Schematic summary of country regulation data compiled from Tables 1 - 2 (a) The levels of animal welfare review carried out across the 13 countries included in this survey: Belgium, Canada, China, France, Germany, India, Iran, Japan, Mexico, the Netherlands, Russia, the United Kingdom (UK), and the United States of America (USA). All surveyed countries have a local animal welfare review committee designated to review animal research protocols and procedures. Some (N = 5) of these countries (France, India, Iran, the Netherlands, the UK) also have a national animal welfare review committee that is involved in animal research project authorization. (**b**) The extent of similarity across different table sections is shown for each of the 13 countries reviewed. There is a consensus on seeking project authorization, regulatory oversight, providing physical enrichment, following a humane method of euthanasia, implementation of the 3Rs*, placing limits on the overall discomfort of animals and, following strict guidelines, fluid control may be permissible (reflected by the darker green 'Yes' circles). The use of wild-caught NHPs for neuroscience research purposes is largely banned, except in India and the USA (see main text for comment). *The 3Rs is an acronym for Replacement, Reduction and Refinement, three key principles used to promote animal welfare in scientific research, originally proposed by Russell and Burch (1959).

Table 1
Overview of ethical regulations for conducting neuroscience procedures in non-human primates (macaques and marmosets).

Country	What committees review and approve a non-human primate (NHP) neuroscience research application?
Section A	Local Committee for Animal Welfare Review
Belgium	**Yes,** a local animal ethics committee reviews, and provides approval for all animal protocols, including NHPs. Committee members are composed of veterinarians, researchers, statisticians, caretakers, medical doctors, legal experts, and ethicists. Some committee members work at a university, while others are not linked to a university.
Canada	**Yes,** in most institutions each protocol is reviewed by one (institutional) or two (facility-based and institutional) committees.
China	**Yes,** two levels of review exist, including a primate Institutional Animal Care and Use Committee (IACUC) at an institute and a university IACUC at medical school. Primate IACUC: head veterinarian, institutional officer, four Principal Investigators (PIs) conducting animal research, and one person from the community who is not a scientist or involved in research. The university IACUC has up to 24 members including a Vice President, Secretary, Director of Facilities, Director of Animal Facilities, head veterinarian, and PIs from medical school, other colleges, and hospitals (see Chinese ethical review guidelines in MacArthur Clark and Sun (2020).
France	**Yes,** local ethical committees (CEEA) provide an ethical evaluation of NHP project applications and a recommendation. If the Local Committee (LC) does not approve the NHP project application, the application is not forwarded for ethical evaluation at the national level. Project applications have to comply with national policy on animal research, which is issued by the national steering committee on animal research (CNREEA) and abides by national decrees relating to the ethical evaluation and the authorization of projects involving the use of animals in experimental procedures and their updates. They have to be registered with the secretary of the national steering committee on animal research (CNREEA), hosted by the Ministry of Higher Education, Research and Innovation. They commit to operate in a transparent and independent manner, to render their judgment with complete impartiality, and to guarantee confidentiality. LCs are, at minimum, composed of a veterinarian, a scientist involved in animal research (NHP research when relevant), a technician involved in animal research (NHP research when relevant), an animal caregiver, and a lay person naïve to animal research. Eight to 10 people usually serve on a LC.
Germany	**Yes**, a LC is tasked with evaluating the ethical aspects of a research project application. Together with an ethical assessment by the animal welfare officer of the research institution, the application is submitted to the local authorities, or regional council (Regierungspräsidium). There the approval decision is guided by a voluntary and independent commission consisting of members, including veterinarians, medical and scientific expertise for animal experiments, as well as representatives of animal protection organizations (German legislation source: *Tierschutzversuchstierverordnung; § 42 Tierversuchskommissionen)*.
India	**Yes**, ethical committee at the institutional/organizational level; an Institutional Animals Ethics Committee (IAEC), comprising of at least 8 members: • Five members from the establishment: (i.e., a biological scientist, chairperson, two scientists from different biological disciplines, a veterinarian involved in the care of animals, and the scientist in charge of the establishment's animal facility) • Three members from outside the establishment: one scientist from outside the institute, a non-scientific socially aware member and a representative or nominee of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) will review and recommend a non-human primate (NHP) research protocol for consideration of CPCSEA. Establishments engaged in research and education involving animals are required to comply with the various guidelines, norms and stipulations set out by CPCSEA. The minimum qualification for the IAEC members is as follows: (i) B.V.Sc. or (ii) M.Sc. (Zoology/Animal Sciences/Animal Biotechnology), or (iii). M.Sc. (Life Sciences/Biological Sciences/Biochemistry/Biotechnology) with experience in animal handling and animal research or (iv) M. Pharm. with experience in animal handling and animal research or (v) M.D. (Microbiology and Pharmacology) with experience in animal handling and animal research. The minimum qualification for the Socially Aware nominee should be at least a graduate, from any subject. Preference will be given to those with a background in Biological Sciences. Having a veterinarian in IAEC is mandatory for judging level of care and handling of laboratory animals in each protocol. In addition to the above IAEC members, a specialist may be co-opted from a relevant field to provide expertise, while reviewing special projects (animal experimental protocol using hazardous agents, such as radioactive substances and deadly microorganisms).
Iran	**Yes,** a local ethical committee reviews each application. The members of the committee are technicians, scientists, and persons who are not professionally involved in animal research and are non-affiliated. The approval of this committee is necessary for starting a research project. The committee is empowered to suspend a project if it finds noncompliance with the policies.
Japan	**Yes**, a local IACUC reviews submitted protocols. The IACUC usually includes other scientists and lay people. Veterinarians are not mandatory committee members.
Mexico	**Yes,** a local ethics committee, composed of veterinarians, technicians, and other scientists, approves research applications.
Netherlands	**Yes,** the institutional Animal Welfare Body (IvD) is the first committee to review an application. The IvD members are animal welfare officers, technicians, and other scientists. The IvD's official duties are to: • Advise staff who deal with animals on animal welfare issues; • Advise staff on the 3Rs and related technical and scientific developments; • Establish and review internal procedures; • Monitor the development and outcome of projects; • Advise on possible adoption schemes. If the IvD supports an application, they advise the Animal Ethics Committee (DEC) on their independent review of the application. It is the DEC that ultimately advises the national ethics committee (Central Authority for Scientific Procedures on Animals; CCD), which decides whether a license will be granted. In their advisory reports to the CCD, DECs use criteria that are set out in legislation. There are currently about 25 DECs in the Netherlands. These are affiliated with the Netherlands Association of Animal Ethics Committees (NVDEC). A DEC consists of at least seven members, with expertise in the various areas of scientific disciplines and scientific applications for which animals are to be used. This includes Replacement, Reduction and Refinement (3Rs) in these fields; Experimental design (including statistical aspects); The practice of laboratory animal medicine or, where necessary, veterinary practice with wild-caught animals; Keeping, caring for, and treating animals of those species that are to be used; Ethics; Laboratory animals and their protection. At least two members are not professionally involved in animal procedures. Nor, in addition to the Chairman, should at least half of the members have any employment relationship with the establishment licensee of the project, for which an advisory report is issued.
Russia	**Yes**, local bioethics commissions carry out approvals of projects with primates. The commissions are composed of researchers with competencies in various fields. There is often a clear deficit in understanding the principles of working with primates.
UK	**Yes**, the local Animal Welfare Ethical Review Body (AWERB) at each institution (e.g. universities, contract research organizations, and NHP breeding centers) provides an evaluation of a NHP research application and a recommendation. If the AWERB does not approve an application, it is not forwarded to the next stage. Between 8 and 12 people usually serve on an AWERB committee and are, at minimum, composed of a Named Veterinary Surgeon (NVS), Named Animal Welfare and Care Officer (NACWO), a scientist involved in animal research (NHP research when relevant), Establishment Licence Holder from the institution, a secretary, and public representative (lay persons). All project licenses authorizing scientific procedures with animals come under the *UK Animal (Scientific) Procedures Act 1986* and *EU Directive 2010/EU/63*. The Secretary of State for the Home Department provides authorization of the regulated procedures carried out on animals. The project license is a legally binding document.
USA	**Yes**, local IACUCs are required by Public Health Service (PHS) regulations and the Animal Welfare Act (U.S. Dept. of Agriculture; USDA). IACUCs should consist of at least 3–5 members: one veterinarian, one practicing scientist experienced in animal research, one member whose primary concerns are non-scientific and/or one non-affiliated member (https://olaw.nih.gov/resources/tutorial/iacuc.htm).
Country	What committees review and approve an NHP application?
Section B	National Committee for Animal Welfare Review
Belgium	**No,** there is an overarching reflections committee that provides oversight and guidelines for NHP research, but it does not approve individual NHP research applications.

(*continued on next page*)

Table 1 (*continued*)

Country	What committees review and approve an NHP application?
Section B	National Committee for Animal Welfare Review
Canada	**No**, there is a national council, the Canadian Council on Animal Care (CCAC) that conducts inspections, provides guidelines and handles compliance issues, but it does not approve individual NHP research applications.
China	**Not applicable.**
France	**Yes**, a group of experts, nominated by the Ministry of Higher Education, Research and Innovation, in charge of evaluating elementary compliance and issuing final approval, on the basis of the initial screening by the local ethical committees. This group of experts works in close interaction with the National Steering Committee on Animal Research (CNREEA). This group is composed of five experts nominated by the Ministry of Higher Education, Research and Innovation and the Ministry of Agriculture, and other scientists and technicians with expertise in animal research.
Germany	**Not applicable.**
India	**Yes**, for carrying out an experiment on NHPs, approval of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) is a must and IAEC may only recommend the research protocol for consideration by CPCSEA. CPCSEA is a statutory body under the PCA (Prevention of Cruelty to Animals) Act 1960 and Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998, Government of India. This body consists of nominated members and representatives from national regulatory agencies (i.e., Ministry of Health and Family Welfare, Ministry of Environment and Forests), national academic and research councils, premier research institutes, eminent scientists, and animal welfare organizations. The duty of the committee is "to take all such measures as may be necessary to ensure that animals are not subject to unnecessary pain or suffering before, during or after the performance of experiments on them." Investigators whose proposals are to be discussed are called to present their case to the IAEC/CPCSEA committees to offer clarifications, if needed. Independent consultants/experts will be invited to offer their opinion on specific research proposals, if needed.
Iran	**Yes,** regulatory and fundamental guidelines for the proper conduct of animal experiments must follow those from the Ministry of Health and Medical Education and the Ministry of Science, Research, and Technology (https://ethics.research.ac.ir/AnimalLabs.php).
Japan	**Not applicable.**
Mexico	**No**, there is a national committee of veterinarians, technicians, other scientists, lawyers, and academic representatives that set the policy for the use of NHPs within institutions and provide guidelines, but it does not approve individual NHP research applications.
Netherlands	**Yes**, the Central Authority for Scientific Procedures on Animals (CCD) is the only body that is authorized to grant project licenses to conduct animal procedures. The CCD is a quasi-autonomous non-governmental organization (QUANGO), appointed by the Ministry of Economic Affairs. Legislation stipulates that the CCD is independent and impartial.
Russia	**Not applicable.**
UK	**Yes**, the Animals in Science Committee (ASC) provides independent advice to the Home Office Inspectors and Secretary of State. The committee consists of up to 12 members with relevant expertise in animal welfare and care, scientists, those with veterinarian training, and lay persons. Each Principal Investigator (PI) responsible for the project license has to participate in an interview with the ASC to answer questions about the application (www.gov.uk/government/organisations/animals-in-science-committee).
USA	**Not applicable.**
Country	What committees review and approve an NHP application?
Section C	Are there any other committees (in addition to the Local and National Committees) that provide advice before final approval?
Belgium	**Not applicable.**
Canada	**Not applicable.**
China	**Yes**, the university IACUC and, where relevant, special protocol committees (e.g., Neuroimaging Center Protocol Committee).
France	**Yes**, the national steering committee on animal research (CNREEA) issues recommendations and enforces the ethics and deontology of animal research, and promotes all methods that are susceptible to improving animal welfare in animal research. The national steering committee on animal research (CNREEA) is composed of scientific experts in animal research from the public sector, scientific experts in animal research from the private sector, experts from the human medical field, veterinarians, experts in philosophy, law, sociology and animal welfare representatives.
Germany	**Yes**, animal research in Germany is guided by the European Directive 2010/63/EU and the Animal Welfare Experimental Animal Ordinance (TierSchVersV). Regional councils must manage commissions accordingly and should also consider Paragraph 15 of the Animal Welfare Act (TierSchVersV § 8, § 9) and Paragraph 11 of this law outlines the permit procedure for breeding and housing animals for scientific purposes.
India	**Not applicable.**
Iran	**Yes**, the network of NHP labs and researchers provides advice and can suggest changes or further justifications for the use of procedures. All procedures were in accordance with international guidelines, such as the Guide for the Care and Use of Laboratory Animals (US National Research Council, 2011) and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.
Japan	**Yes**, many institutes perform monkey research using Japanese monkeys, which are distributed by the National BioResource Project (NBRP; https://nbrp.jp/en/resource/japanese-macaques-en/). Research using these monkeys must be approved by the NBRP Council composed of other scientists.
Mexico	**Not applicable.**
Netherlands	**Yes**, covered above in Section A.
Russia	**Yes**, experts of the Russian Laboratory Animal Science Associations (RUS-LASA) offer independent assessment (on demand) services for those interested in serious expertise in research projects involving primates.
UK	**Yes**, a subgroup of Home Office Inspectors (HOIs) with NHP expertise linked to the Animals in Science Regulation Unit (ASRU) provide advice, and can request further justification for the use of NHPs and procedures. The ASRU is responsible for administering and enforcing *The Animals (Scientific Procedures) Act 1986 in England, Scotland and Wales* (see UK Home Office Collection at gov.uk).
USA	**No**, as part of the application a section on vertebrate animals has to be filed, which contains all relevant information on the procedures that the laboratory animals will undergo. The review panel discusses this section along with the application. If the procedures detailed in the application do not meet ethical standards, it will not get funded. Approval by the local IACUC is necessary in order to receive federal support.
Country	What do they consider during their approval process?
Section D	Implementation of the 3Rs (Replacement, Reduction, Refinement)
Belgium	**Yes**, each project should be in accordance with the Guide for the Care and Use of Laboratory Animals (US National Research Council, 2011) and European guidelines (*Directive 2010/63/EU*). • Experimenters have to prove adequate training and the 3Rs have to be considered in each protocol. • The necessity of using NHPs compared to other animal species and humans has to be shown. • The number of proposed animals has to be justified. • The origin of the animals has to be shown (at least second generation bred by authorized NHP breeders). • NHP projects have to follow the recommendations of the Weatherall Report (Weatherall et al., 2006). • Animals need to be allowed extensive locomotor behavior, foraging, and social interactions. • The intended treatment and care (including housing) before, during and after the procedure, as well as the expertise of the responsible individuals is considered. • The nature, frequency and duration of the procedures to which the animal is to be subjected as well as the degree of distress and discomfort that the laboratory animals will (or may) experience.

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Table 1 (*continued*)

Country	What do they consider during their approval process?
Section D	Implementation of the 3Rs (Replacement, Reduction, Refinement)
	• The use (or potential use) of anesthesia, analgesics and other methods to avoid distress and discomfort, and whether a given animal was previously used for a procedure. • Additionally, whether, and – if so – at what time, it was decided to proceed with the responsible sacrifice of the laboratory animals involved and the method used on that occasion. • The final destination of the animal after the procedure is also considered.
Canada	**Yes**, the committees request information on how a specific submission or an ongoing protocol considers the 3Rs. The committees comment and request modifications in cases where accounting for the use of 3Rs is incomplete.
China	**Yes**, justification for the use of NHPs, the number of NHPs, and the procedures to minimize distress are addressed in each protocol. Regular training courses are offered that every user must take. This includes the 3Rs (*Animal Welfare Act, Guide to Lab Animals*), animal husbandry, animal use (surgery, anesthesia, physiology, behavioral training, water regulation, animal endpoint criteria), biosafety, personnel safety and personal protective equipment (PPE), protocols and forms, and compliance.
France	**Yes**, this involves justifying the number of animals used, including an appropriate power analysis. Explanations are required for refinement actions taken and justify, if necessary, why available refinement actions may not be taken. There is also consideration about whether replacement techniques are available or not.
Germany	**Yes**, under the European Directive 2010/63/EU, researchers must replace animal studies with other research methods wherever possible; employ strategies that will reduce the number of animals insofar as maintaining scientific rigor; and refine experimental and husbandry procedures to minimize potential pain or distress for the animals. The necessity of using NHPs compared to other animal species and humans has to be shown.
India	**Yes**, IAEC and CPCSEA ensure the concept of 3Rs: reduction, refinement and replacement. In the case of experimentation involving large animals, a fourth R is considered - rehabilitation - aimed at minimizing the welfare costs to animals used in research. Animals lowest on the phylogenetic scale (i.e., with the least degree of sentience), which may give scientifically valid results, should be used for any experimental procedure. Experiments are expected to be designed with the minimum number of animals to give statistically valid results at 95% level of confidence. Alternatives not involving animal testing should be given due and full consideration and sound justification provided, if alternatives, when available, are not used. PIs engaged in animal experimentation have a moral responsibility for the welfare of the animals during and after their use in experiments. Investigators are responsible for the aftercare and/or rehabilitation of animals after experimentation and may be permitted to euthanize under special circumstances mentioned in the CPCSEA guidelines. Costs of aftercare and/or rehabilitation of an animal's post-experimentation are to be part of research costs and should be scaled per animal in positive correlation with the level of sentience of the animals. Nominees can visit and check the animal house without prior notification at any time whenever possible to ensure the welfare of animals.
Iran	**Yes**, PIs must complete a research protocol that addresses model selections and 3Rs concerns. PIs should provide enough evidence from the literature to show the significance of research and the necessity of animal selection. All engaged researchers should take regular training workshops on working with animals.
Japan	**Yes**, 3Rs must be described. This involves: • Justifying the number of animals used; • Including an appropriate power analysis; • Explanation of refinement actions taken; • Justification, if necessary, why available refinement actions may not be taken; • Discussing whether replacement techniques are available or not.
Mexico	**Yes**, Mexico is close to fully implementing the 3Rs. Clear measures for refinements have been implemented over the past ten years and all the surgical, recording and training protocols follow the principles outlined in the Guide for Care and Use of Laboratory Animals (*NIH, publication number 85–23, revised 1985*).
Netherlands	**Yes**, the CCD and DEC examine various aspects of the project plan: • The expertise of the individual who determines the design and implementation of the procedure; by whom, or by which committee, the procedure's scientific quality is assessed. • The reasoning used to answer the question of why the procedure cannot be performed with fewer laboratory animals, or by using a technique that does not involve the use of laboratory animals at all (3Rs). • The reasons given for selecting the species and number of laboratory animals to be used. • The origin of the laboratory animals to be used. • The intended treatment and care (including housing) before, during and after the procedure, as well as the expertise of the responsible individuals. • The nature, frequency and duration of the procedures to which the animal is to be subjected. • The degree of distress and discomfort that the laboratory animals will (or may) experience. • The use (or potential use) of anesthesia, analgesics and other methods to avoid distress and discomfort. • Whether a given animal was previously used for a procedure. • Whether, and – if so – at what time, it was decided to proceed with the responsible sacrifice of the laboratory animals involved and the method used on that occasion. • The final destination of the animal after the procedure.
Russia	**Yes**, approval forms include an obligatory section describing 3Rs implementation: • Explanation of the necessity of using NHPs; • Sample size evaluation and power analysis; • Description of housing conditions; • Enrichment; • Qualification of researchers involved in the project; • Severity assessment.
UK	**Yes**, "*under the Animals (Scientific Procedures) Act 1986 section 5B(3)(b), in carrying out the evaluation of the programme of work, the Secretary of State must assess the compliance of the programme of work with the principles of replacement, reduction and refinement (*3Rs*). These principles are described in section 2A(2) of the Act*" (source: *UK Home Office Project License application form*). In addition, the evaluation includes justification for the species and the numbers of animals used, including appropriate power analysis. Explain refinements to procedures used and actions to be taken, and justify, if necessary, why available refinements may not be used. Discussion on whether reduction and/or replacement techniques are available or not.
USA	**Yes**, local animal research protocols usually contain a question asking about how the PIs' selection of the model considers the 3Rs, and often require a detailed literature search documenting the necessity of the animal model.
Country	What do they consider during their approval process?
Section E	Project authorization
Belgium	The Animal Ethics Committee determines whether experiments on animals meet legal requirements (according to the latest national guidelines and EU Directive). The Animal Ethics Committee has the following responsibilities: • Evaluating proposed and completed experiments; • Establishing ethical standards for experiments on animals; • Providing advice to the laboratory director, experiment coordinators and assistants on the ethical aspects of experiments on animals; • Providing advice to the supervisory authorities on ethical aspects of experiments on animals. • Gather information and/or advice (both from within and outside the applying institution) to aid in performing committee duties.

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Table 1 (*continued*)

Country	What do they consider during their approval process?
Section E	Project authorization
Canada	Project authorization is contingent upon the ethical approval, training and certification of the experimenters for conducting animal research, and compliance with regular inspections conducted by the local compliance officer.
China	Protocols and amendments are thoroughly reviewed; responses to any questions must be addressed in writing by PIs and re-reviewed by committee. Compliance consists of unannounced inspections of labs (once per year). Failure to address non-compliance is met with removal of privileges (e.g., animal facility keycard inactivated, no approval to purchase animals or drugs). If there is a sustained pattern of non-compliance, the user will be barred from the institute.
France	An animal welfare body is constituted in every research center, composed of the research center appointed veterinarian, scientists and technicians. It is responsible for the continuous monitoring of project progress relative to project authorization, approving minor changes in the research project and referring to the local ethical committee, CEEA, in case of major change. The welfare body is responsible for the retrospective analysis at the end of the project, together with the local ethical committee (CEEA). Meetings and efficiency of animal welfare bodies is controlled once a year by departmental state inspection. Annual departmental state inspection (DDPP) verifies that all ongoing research projects are properly authorized, implemented and retrospectively evaluated.
Germany	Project authorization is contingent upon the ethical approval and competency of the experimenters and their certifications for conducting animal research (i.e., FELASA B, laboratory animal training course).
India	NHPs research protocols are reviewed by IAEC and approved by CPCSEA. Justifications to any questions must be addressed by PIs and re-reviewed by the committees. Nominees will visit animal houses at least once in a calendar year to look at the wellbeing and maintenance of animal and relevant record books and submit the annual report to the CPCSEA office. CPCSEA can act against an establishment or breeder, based on the report of the Member Secretary or authorized officer, regarding any violation of the rules, or of committee directions. In case of a major violation, CPCSEA may issue written orders, suspend or revoke the registration of the establishment and/or order closure of the animal house facility, after giving the establishment or breeder an opportunity of being heard in the matter.
Iran	The approval of an ethical committee is required by grant agencies; furthermore, the local veterinarian checks the animal welfare regularly.
Japan	Each project is approved based on cost benefit, especially anticipated contribution of the research objectives to science and medicine. All research projects and laboratory facilities are regularly approved.
Mexico	Checks on facilities by national committees occur sporadically (approximately once every five years), the local ethics committee performs checks every year, and the day-to-day running is supervised by the local veterinarians.
Netherlands	The institutional Animal Welfare Body (IvD) requires a Study Dossier for individual studies once a project has been granted by the CCD. They also carry out the day-to-day checks and often require periodic progress reports.
Russia	Project authorization based on detailed review of the application form by the local ethics committee (LC). In general, no post-approval project inspection occurs, but common practice is annual inspections of animal facilities by the LC.
UK	Regular meetings with the Named Veterinary Surgeon (NVS) and Named Animal Welfare and Care Officer (NACWO) are held to ensure the project is on course and if any changes have to be implemented. May require protocol and procedure changes to project license. These changes require approval from AWERB, and sometimes ASC. They also require Home Office Inspector (HOI) authorization and sign off from the Secretary of State for the Home Department. AWERB is also responsible for the retrospective analysis halfway through the project (typically at the two-year stage) and at the end of the project. These retrospective reviews are submitted to the Home Office (www.health-ni.gov.uk/publications/animal-scientific-procedures-retrospective-assessment-guidance). The regional HOI will undertake regular, unannounced visits and may access any records, as requested.
USA	By Federal regulation, IACUCs are charged with biannual inspections of animal housing and animal use areas. Post approval monitoring of procedures happens in this context. This is an ongoing issue at some universities – how to do post IACUC protocol approval monitoring of procedures. USDA covered species (all vertebrate, or warm-blooded, animals except rats, mice and birds) protocols are reviewed every year. All others are reviewed every 3 years.
Country	What do they consider during their approval process?
Section F	Harm/Benefit Analysis (HBA) - refer back to the main text for a complete explanation of the harm/benefit analysis.
Belgium	Refer to consideration of 3Rs implementation as well as the origin, severity, re-use and group housing of NHPs; harm/benefit analysis also weighs surgical, analgesic, anesthesia, and water regulation procedures. An estimate of discomfort is required as well as an estimate of the cumulative discomfort throughout the study.
Canada	Harm/benefit is implicitly considered by the funding agencies during the review of submitted funding applications. A second stage considering harm/benefit is at the Facility Animal Care Committee and the Institutional Animal Care Committee.
China	The procedures that can be considered 'harmful' are surgery, anesthesia, housing, and water regulation. To weigh the harms and benefits, specific questions are asked. Do surgical anesthesia and analgesia procedures follow NIH regulations? What defines the study endpoint? If housed singly, what are the considerations of social benefit vs. injury due to fighting. For water regulation, what is the minimum volume per day, and how is animal health monitored? What kinds of enrichment is provided (e.g. foods, toys, TV, tasks related to study goals, time in a larger play cage). Sometimes the value of the proposed research and whether the same work can be done in a different species is additionally discussed.
France	There is no explicit harm/benefit assessment. However, harm/benefit assessment is at the root of ethics. It is thus embedded in the 3R assessment as well as in the scientific justification of the project. Harm/benefit assessment is also embedded in the retrospective analysis performed at the end of the project.
Germany	At the time of protocol review and pending approval, the harm-to-benefit ratio is assessed.
India	The Principle Investigator (PI) must ensure that the procedures, which are considered painful, are conducted under appropriate anesthesia and analgesia as recommended in the CPCSEA guideline. Rationale for animal usage will be discussed during the IAEC meeting with the following points: (1) Why is animal usage necessary for these studies? (2) Why are the particular species that are selected required? (3) Why is the estimated number of animals essential? (4) Are similar experiments conducted in the past? If so, the number of animals used and results obtained in brief. (5) If yes, why is a new experiment required? (6) Have similar experiments been made by any other agency? If so, their results in your knowledge. These points should be clearly justified by the PI before getting NHP protocol approval from the CPCSEA.
Iran	During the protocol review, the local committee discusses the harm and benefits of the research. Our routine laboratory procedures include housing the primates in a large space with sunshine, providing them with an enriched environment (TV and toys), and frequent contact with other animals (visual, auditory, touch and grooming).
Japan	The validity of an animal experiment is judged by a harm/benefit analysis of pain/distress experienced by animals and the significance (outcome) of the experiment. Depending on the nature of the research being conducted, the degree of pain/distress experienced by animals is grouped into 5 categories. When preparing an animal experiment protocol, the Principal Investigator (PI) must fully understand which pain category the protocol falls into.
Mexico	The assessment is mainly performed on the structure of the protocols.
Netherlands	The harm/benefit analysis is an integral part of the application procedure. For each intended procedure and potential consequence, an estimate of discomfort is required as well as an estimate of the cumulative discomfort throughout the study. Both the scientific and societal benefits that are to be expected from the study have to be specified.
Russia	Researchers have to specify (1) particular applied or fundamental scientific problem which will be addressed by the project, (2) qualification and experience available; (3) all animal welfare issues including housing conditions, single/group housing, research procedures; (4) methods of recognizing and assessing suffering.
UK	The costs to the animal in relation to the perceived benefits are used as a basis for deciding if the project license can be approved. This analysis is conducted by the AWERB and, at the national level, by ASRU and the subgroup of NHP HOIs. ASRU guidance is available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/487914/Harm_Benefit_Analysis_2_.pdf. Harm/benefit assessments are also embedded in the retrospective analysis of the project.

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Table 1 (*continued*)

Country	What do they consider during their approval process?
Section F	Harm/Benefit Analysis (HBA) - refer back to the main text for a complete explanation of the harm/benefit analysis.
USA	The IACUC members discuss the harms and benefits of the research at the time of protocol review. This is always done for protocols involving pain that is difficult to relieve, or for animals expected to become sick, or otherwise impaired as a result of the scientific procedure. For some IACUCs, this is also assessed for any experimental procedure.
Country	What do they consider during their approval process?
Section G	Anything else, not covered above?
Belgium	N/A
Canada	N/A
China	N/A
France	N/A
Germany	N/A
India	N/A
Iran	N/A
Japan	N/A
Mexico	N/A
Netherlands	N/A
Russia	There is no current legislation about the ethical approval of animal experiments in Russia. All information in this table describes occasionally developed 'good practice,' implemented in most (not all) scientific organizations working with animals.
UK	N/A
USA	Animal research in the US is governed by Federal legislation – the Animal Welfare Act and the relevant enforcement branch of the USDA, called APHIS (Animal and Plant Health Inspection Service), which oversees animal use and research. Biomedical research funded by the NIH and NSF, or DOD, is under additional regulations as outlined by the PHS of NIH and the enforcement branch OLAW, which covers all vertebrate animals used in NIH-funded research. FDA also provides oversight for its supported research. AAALAC International is a private, non-profit organization that promotes the humane treatment of animals used in scientific research. AAALAC standards exceed those of federal laws and policies, and accreditation by AAALAC International is a clear demonstration of an institution's commitment to the responsible treatment of animals. Many US institutions are AAALAC accredited.

In addition to previously published tables covering these regulations for NHP neuroscience research in China, France, the UK and the USA (Mitchell et al., 2021), we now also include details from the following countries: Belgium, Canada, Germany, India, Iran, Japan, Mexico, the Netherlands and Russia. These tables were developed as a shared resource, highlighting differences and similarities between the regulations already existing in these countries, and made openly available to inform and guide.

1.3. Key ingredients supporting global collaboration in NHP biomedical research

In an attempt to map a pathway to facilitate global collaboration linked to NHP research, we qualitatively analyzed regulatory data and identified five key ingredients linked to these data that we propose will help facilitate international interactions. These include: (1) ***Analyze current ethical decision models;*** (2) ***Identify common ground;*** (3) ***Cooperate with scientists on a global scale***; (4) ***Share and contribute to information resources***; and finally (5) ***Communicate with the public and policy makers***. By following these guiding steps, we may effectively increase awareness about the continued critical importance of, and knowledge and value obtained from scientific research with NHPs.

2. Analyze current ethical decision models

Ethical and welfare standards are typically national affairs. However, the intergovernmental World Organization for Animal Health (WOAH; woah.org/en/home) in 2010 issued common standards, called a Terrestrial Code, that were accepted by all 182 member countries to use when formulating their own national regulations (see Chapter 7.8: Use of Animals in Research and Education). Nevertheless, the WOAH Guiding Principles for Animal Welfare are not a legal declaration, by which member countries must formally abide. Thus, despite this guidance on common standards, NHP researchers interested in pursuing international collaborations still need to adhere to typically multiple, independently formulated guidelines and regulations. An overarching solution would be a unified and agreed upon common set of guidelines, akin to the Helsinki Declaration, but for animal research (see Petkov et al., 2022; World Medical Association, 2001). In lieu of a common framework that is yet to be formulated, a preliminary step is making national regulations accessible, along with the ethical rationale and models driving these regulations.

Currently, the WOAH standards for the use of animals in research, testing, and education stipulates that consideration of the 3Rs (*Replacement, Reduction, and Refinement*; Russell and Burch, 1959) must be conducted during a project proposal review. A shared international ethical declaration for NHP neuroscience research could also be based on the 3Rs (see Fig. 1b), which are the predominant set of principles internationally. Other sets of ethical and moral principles also exist and complement the 3Rs; such as the 6Ps (or 6 Principles of Animal Research Ethics; DeGrazia and Beauchamp, 2019), the 3Vs linked to considerations of the *validity* of research methodologies and the proposed animal model (Eggel and Würbel, 2021), and the 3Ss: *Good Science*, *Good Sense*, and *Good Sensibilities* (Smith and Hawkins, 2016). These additional sets of principles could also be incorporated into a common set of guidelines (e.g. see Petkov et al., 2022).

For the majority of countries included in our review, additional committees operating at different levels are involved in the NHP research application process. This includes application review, authorization, reflection committees, and the ongoing oversight of approved research projects and institutional compliance. During the research project authorization process, ethics and animal welfare committees consider the anticipated contribution of the research objectives to basic science and medicine and whether experiments meet legal requirements. The 3Rs implementation extends across all the countries reviewed here, and the 3Rs are considered during the screening of research project applications. Interestingly, an additional ethical approach - conducting a Harm-Benefit Analysis (HBA) - is also being used in the decision-making process during each countries' review of its NHP research projects.

The HBA, originally proposed by Patrick Bateson (1986), can be applied to assess the potential (or actual) pain, suffering, or distress that an animal may experience as a consequence of being involved in a proposed experimental procedure, against the justifications for these

Table 2
Welfare and other regulations regarding accommodation, care and use of NHPs (macaques and marmosets).

Section A	Use of wild-caught NHPs for research purposes
Belgium	**Banned.**
Canada	**Banned.**
China	**Banned.**
France	**Banned.**
Germany	**Banned.**
India	**Not banned**, but procurement of wild-caught monkeys for research activities requires prior permission from the Principal Chief Conservator of Forest (Wildlife) and Chief Wildlife Warden.
Iran	**Banned.**
Japan	**Banned.**
Mexico	**Banned.**
Netherlands	**Banned.**
Russia	**Banned.** Animals are used which were bred at the Research Institute of Medical Primatology (http://primatologia.ru/en/); the capabilities of this organization cover all NHP stocks in the research community.
UK	**Banned.**
USA	**Not banned**, especially not for field biology work. Purchase of wild-caught animals for biomedical research is strongly encouraged from reputable sources.
Section B	**Inspection of facilities (minimum number)**
Belgium	**Once or twice a year**, of which inspection timing is unpredictable.
Canada	**At least once a year** inspections are carried out by a facility compliance officer. Inspection of an institution's policies and facilities by the Canadian Council on Animal Care is conducted every 3 years (https://ccac.ca/en/guidelines-and-policies/the-guidelines/types-of-animal-guidelines.html).
China	**Once a year.**
France	**Once a year.**
Germany	**Routine inspection**. All facilities are subject to inspections by the designated authorities. These inspections must be done at least every 3 years for facilities conducting animal experiments and every year for facilities conducting procedures on primates (*Animal Protection and Laboratory Animal Ordinance - TierSchVersV § 8, § 9*).
India	**Once a year** by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) nominee.
Iran	**At least once a year**, no specific regulations.
Japan	**Once per 5–7 years** by the Japanese Association of Laboratory Animal Science (JALAS).
Mexico	**Once a year**, no specific regulations.
Netherlands	**Once or twice a year**, of which inspection timing is unpredictable.
Russia	**Once a year**, no specific regulations.
UK	**At least once a year,** of which inspection timing is unpredictable.
USA	**Regular inspection** by the USDA, which is unannounced (unless requested by an institution), and **semi-annual inspection** by the IACUC as required by the Animal Welfare Act (under *§ 2.31(c)*).
Section C	**Single housing**
Belgium	Not allowed, unless temporarily for quarantine or health reasons.
Canada	Cages must be designed for pair or group housing of animals.
China	Single housing of macaques must be an approved exemption by the IACUC. Single-housed macaques must maintain social contact by visualization, hearing and smelling of other monkeys. Veterinarians assess for stereotypies and well-being. Enrichment (e.g., variety of food, toys, music, TV, behavioral training) is provided. Marmosets live in cages that house family groups.
France	Only in exceptional circumstances. Must be approved by the veterinarian and animal welfare body. Must maintain social contact (i.e. visualizing, hearing, smelling other monkeys). Regularly assessed for stereotypies and overall well-being and extra enrichment must be provided.
Germany	Only in exceptional circumstances.
India	Not recommended, if needed, should be justified in the Institutional Animals Ethics Committee (IAEC) protocol and should get approval from the CPCSEA committee. NHP facilities should have a run/play area for free ranging activities. Group housing should be considered for communal animals, where it is important to consider population density and ability to disperse; initial familiarity among animals; and age, sex, and social rank.
Iran	Scientific justification or veterinary exceptions allowed. Primates live in a large space with sunshine and frequent contact with other animals (visual, auditory, touch and grooming).
Japan	Allowed, but paired or group housing is recommended and will become mandatory in 10 years (www.jnss.org/en/animal_primates).
Mexico	Allowed, but paired or group housing is recommended.
Netherlands	Temporarily allowed, but a reason must be provided and it is classified as additional discomfort.
Russia	Allowed. There is an opportunity for visual and sound contact between animals in the common areas of the vivarium.
UK	Only in exceptional circumstances. Must be approved by veterinarian and animal welfare officers. Regularly assessed for stereotypies and overall well-being and extra enrichment must be provided. Must still have visual, auditory, and olfactory interactions with other monkeys.
USA	Scientific justification or veterinary exceptions allowed (e.g. no suitable pairs).
Section D	**Limits of pain, suffering, and distress**
Belgium	Must be defined in protocols and for each procedure. Needs approval and helps to formulate the harm/benefit analysis.
Canada	Must be defined in protocols and for each procedure. This is an important item of project authorization. Requires discussion and decision by animal welfare body.
China	All surgical interventions should be performed under appropriate anesthetic and analgesic agents. Stereotypies (or other behavioral indications of distress) are assessed for treatment either medically, with enrichment, or with social pairing methods.
France	Must be defined in protocols and for each procedure. This is an important item of project authorization. Requires discussion and decision by animal welfare body.
Germany	Must be defined in protocols and for each procedure. Follows the ordinance on the protection of animals used for experimental purposes or for other scientific purposes (*Animal Protection and Laboratory Animal Ordinance - TierSchVersV § 8, § 9*).
India	All surgical interventions should be performed under appropriate anesthetic and analgesic agents. If the experimental protocol prohibits use of anesthetic or analgesics for the conduct of painful procedures (any which cause more pain than that associated with routine injection or blood withdrawal) should be justified with explanation in the IAEC protocol and should obtain approval from the CPCSEA committee. All invasive and potentially stressful non-invasive procedures that animals will be subjected to during the experiments should be listed and described in the IAEC protocol.
Iran	Limits of pain, suffering, and distress must be clarified in protocols. This is one of the requirements for authorizing a research project.
Japan	Must be defined in protocols and for each procedure. Should be approved by the IACUC.
Mexico	Must be defined in protocols and for each procedure.

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Table 2 (*continued*)

Section D	Limits of pain, suffering, and distress
Netherlands	Defined for each procedure separately, as well as cumulatively. Severe discomfort is generally not allowed.
Russia	Limits of pain, suffering, and distress are discussed in detail when preparing applications for local bioethics commissions.
UK	Must be defined in protocols and for each procedure. Needs approval and helps to formulate the harm/benefit analysis.
USA	Limits of pain, suffering, and distress required unless scientifically justified and requires approval by the IACUC.
Section E	**Method of euthanasia**
Belgium	Anesthetic overdose.
Canada	Anesthetic overdose.
China	Anesthetic overdose.
France	Anesthetic overdose.
Germany	Anesthetic overdose.
India	Anesthetic overdose, following specific conditions under which euthanasia is permitted (see CPCSEA guidelines: cpcsea.nic.in/WriteReadData/userfiles/file/Compendium%20of%20CPCSEA.pdf). Rehabilitation is recommended for large animals like NHPs whenever possible. See also Section T for further details.
Iran	Anesthetic overdose.
Japan	Anesthetic overdose.
Mexico	Anesthetic overdose.
Netherlands	Anesthetic overdose.
Russia	Anesthetic overdose.
UK	Anesthetic overdose.
USA	Anesthetic overdose, following guidelines set by the American Veterinary Medical Association (AVMA).
Section F	**Weaning age macaques (separation from the mother)**
Belgium	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
Canada	Not before 10 months of age.
China	N/A
France	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
Germany	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
India	Not before 9–12 months of age (followed in Primate Research Labs, PRLs).
Iran	Not before 8 months of age.
Japan	Not before 1 year of age.
Mexico	Not before 10 months of age.
Netherlands	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
Russia	Not before 8 months of age (*GOST 33218-2014 [state standard], based on the European Union Directive 2010/63/EU*).
UK	Not before 8 months of age.
USA	N/A
Section G	**Weaning age marmosets (separation from the mother)**
Belgium	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
Canada	Not earlier than 8 months of age.
China	N/A
France	Not before 6 months of age, but as a member of the European Parliament, follows Directive 2010/63/EU (not before 8 months of age).
Germany	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
India	N/A
Iran	N/A
Japan	Depending on the institute.
Mexico	N/A
Netherlands	Not before 8 months of age (*Directive 2010/63/EU of the European Parliament*).
Russia	Not before 8 months of age (*GOST 33218-2014 [state standard], based on the European Union Directive 2010/63/EU*).
UK	From 8 months of age.
USA	From 6 to 8 months of age.
Section H	**Cage size for macaques in experiments: minimum volume per adult animal (>3 years)**
Belgium	1.8 m × 1.8 m x 1.8 m
Canada	Cages must be designed for pair or group housing of animals, such that normal affiliative behavior and avoidance behavior can be expressed, and negative interactions reduced. Cages must provide sufficient space, both horizontally and vertically, to allow adequate freedom of movement for the animals to perform positive physical and social behaviors important to their welfare (e.g., grooming, resting, foraging, play, normal locomotor repertoire), while reducing the incidence of negative behaviors.
China	1.0 m × 0.9 m x 0.7 m
France	1.8 m × 1.8 m x 1.8 m
Germany	1.8 m × 1.8 m x 1.8 m
India	Minimum floor area and height recommended for monkeys based on their weight (size) and behavioral activity. For animals up to 3–10 kg: 4.3 ft^2 x 6 ft = 25.8 ft^3 (*CPCSEA Compendium, 2018: Annexure 3E, page 85*). In PRLs, experimental animal cage volume: 4.5 ft × 4 ft x 6.5 ft = 117 ft^3 for two animals.
Iran	Depends on animal weight (size), but typically around 1.0 m × 1.0 m x 1.8 m.
Japan	Minimum housing space per macaque: body weight (kg)/floor space per animal (m^2)/height (cm): 0.0–1.5/0.20/76.2; 1.5–3.0/0.28/76.2; 3.0–10.0/0.40/76.2; 10.0–15.0/0.56/81.3; 15.0–20.0/0.74/91.4 (www.jnss.org/en/animal_primates).
Mexico	1.1 m × 1.1 m x 1.1 m
Netherlands	1.8 m × 1.8 m x 1.8 m
Russia	1.8 m × 1.8 m x 1.8 m (*GOST 33218-2014 [state standard], based on the European Union Directive 2010/63/EU*).
UK	1.8 m × 1.8 m x 1.8 m
USA	Depends on weight of the animal; for a monkey up to 15 kg, floor size at least 6 ft^2 (0.56 m^2), as per United States Department of Agriculture (USDA) requirements (citation *9 C.F.R. § 3.75 – 3.92*).
Section I	**Cage size for macaques in experiments: minimum enclosure height**
Belgium	1.8 m
Canada	Consideration must be given to providing the animals a complex environment with sufficient horizontal and vertical space for unhindered species-specific behaviors suited to the age and health status of the animals. NHPs must be provided with perching or elevated areas and other opportunities for species-typical behaviors.

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Table 2 (*continued*)

Section I	Cage size for macaques in experiments: minimum enclosure height
China	0.8 m
France	1.8 m
Germany	1.8 m
India	Minimum floor area and height recommended for monkeys based on their weight (size) and behavioral activity: 6 ft (1.83 m) is recommended by the CPCSEA Compendium for an animal with body weight up to 15 kg (source: *Annexure - 3E page No. 85*). In PRLs, experimental animal enclosure height: 6.5 ft (1.98 m).
Iran	1.8 m
Japan	0.76–0.91 m (depending on body weight).
Mexico	1.2 m
Netherlands	1.8 m
Russia	1.8 m (*GOST 33218-2014 [state standard], based on the European Union Directive 2010/63/EU*).
UK	1.8 m
USA	Depends on the weight of the animal. For a monkey up to 15 kg, at least 32 inches (2.67 ft or 0.81 m) high.
Section J	**Cage size for marmosets in experiments: minimum volume per animal (>5 months)**
Belgium	Floor area 0.5 m^2 (for 1-2 marmosets), minimum volume per additional animal 0.2^3 (*Directive 2010/63/EU of the European Parliament*).
Canada	Minimum floor area 0.5 m^2 (for 1-2 animals); minimum additional volume per animal 0.2 m^3.
China	No national standard, dependent on the institute, e.g., using 1.0 m × 1.0 m x 2.5 m cages for a family group.
France	Floor area 0.5 m^2 (for 1-2 marmosets), minimum volume per additional animal 0.2^3 (*Directive 2010/63/EU of the European Parliament*).
Germany	Floor area 0.5 m^2 (for 1-2 marmosets), minimum volume per additional animal 0.2^3 (*Directive 2010/63/EU of the European Parliament*).
India	N/A
Iran	1.0 x 1.0 × 2.0 m cages for a family group.
Japan	Floor space/animal: 0.20 m^2; height 76.2 cm. For individual housing, it is advisable that wider and taller cages be used. It is advisable that the ceiling of the cage be set higher than human eye level (www.jnss.org/en/animal_primates).
Mexico	N/A
Netherlands	Floor area 0.5 m^2 (for 1-2 marmosets), minimum volume per additional animal 0.2^3 (*Directive 2010/63/EU of the European Parliament*).
Russia	0.2 m × 0.2 m x 0.2 m
UK	0.2 m × 0.2 m x 0.2 m
USA	Floor area per animal (<1 kg) is 0.15 m^2 (or 1.6 ft^2), as per United States Department of Agriculture (USDA) requirements (citation *9 C.F.R. § 3.75 – 3.92*).
Section K	**Cage size for marmosets in experiments: minimum enclosure height**
Belgium	1.5 m
Canada	1.5 m
China	2.5 m
France	1.5 m
Germany	1.5 m
India	N/A
Iran	2.0 m
Japan	0.76 m
Mexico	N/A
Netherlands	1.5 m
Russia	1.5 m
UK	1.5 m
USA	0.508 m (or 20 inches)
Section L	**Double-tiered caging**
Belgium	Animals are pair-housed in larger groups; this includes large play areas (16–32 m^2) with extensive cage enrichment and tools.
Canada	Animals are pair-housed in large cages that include a play area and multiple sitting levels.
China	Animals rotate through large play cages.
France	NHPs cannot live in double-tiered caging. Allowed by animal welfare body for short periods due to health or experimental requirements.
Germany	NHPs cannot live in double-tiered caging. Allowed by animal welfare body for short periods due to health or experimental requirements.
India	N/A
Iran	N/A
Japan	Recommended.
Mexico	N/A
Netherlands	Animals are pair-housed in large cages that include a play area and multiple sitting levels.
Russia	No specific regulations.
UK	Allowed as outpens, but NHPs cannot live in double-tiered caging for long periods of time.
USA	N/A
Section M	**Grid flooring**
Belgium	None, use dry bedding (i.e., hay).
Canada	N/A
China	N/A
France	Not allowed.
Germany	Solid floors preferred (and used). Exceptions for short-term allowed on compelling scientific or veterinary reasons (e.g. first 24 h after neurosurgery).
India	N/A
Iran	N/A
Japan	No specific regulations.
Mexico	N/A
Netherlands	Solid floors preferred (and used).
Russia	Solid floors (*GOST 33218-2014 [state standard], based on the European Union Directive 2010/63/EU*).
UK	Not allowed long-term. Exceptions for short-term allowed on compelling scientific or veterinary reasons (e.g. first 24 h after neurosurgery).
USA	N/A
Section N	**Physical enrichment**
Belgium	**Yes**, extensive, varying cage enrichment.
Canada	**Yes**, housing should offer a variety of activities and resources for animals to explore.
China	**Yes.**

(*continued on next page*)

Table 2 (*continued*)

Section N	Physical enrichment
France	**Yes**, it should be extensive, include novelty and regularly assessed by animal welfare bodies.
Germany	**Yes**, it should be incorporated.
India	**Yes.**
Iran	**Yes**, there is physical and psychological enrichment.
Japan	**Yes**, recommended.
Mexico	**Yes**, recommended.
Netherlands	**Yes.**
Russia	**Yes**, limited use.
UK	**Yes**, it should be present.
USA	**Yes**, enrichment plans are required per institution. These plans include psychological enrichment as well as exercise and physical enrichment.
Section O	**Fluid control**
Belgium	**Allowed**. By a minimum of 20 mL/kg/day. Use 100 mL per day on the weekends with additional fruits (i.e., apples, bananas, carrots). Strict protocols apply.
Canada	**Allowed**. Each application of fluid intake regulation must be thoroughly described and scientifically justified, and be approved by the animal care committee. For each fluid intake regulation protocol, the minimum level of regulation for each individual animal that will produce the required behavioral performance for the experiment and maintain the animal's health must be used.
China	**Allowed**. By a minimum of 20 mL/kg/day. Require one day of ad libitum per week. Must justify and explain methods of monitoring health and welfare. NHPs are weighed daily. At 15% weight loss from baseline, the animal must be reviewed by a veterinarian; at 20% weight loss from baseline, the animal is taken off of study.
France	**Allowed**. By a minimum of 20 mL/kg/day. Require one day of ad libitum per week (*EU Directive 2010/63/EU*). Animal welfare must be assured as assessed by the animal welfare body. Must weigh monkeys daily; working weight should be stable. Best practice enforced by animal welfare body should follow the recommendations of the national steering committee on animal research (CNREEA), which is based on the GDR Biosimia recommendation (French research group on NHPs in biomedical research; https://gdr-biosimia.com) and the UK National Centre for 3Rs (NC3Rs) recommendations (nc3rs.org.uk/refining-food-and-fluid-control-behavioural-neuroscience-macaques; Prescott et al., 2010; Gray et al., 2016, 2019).
Germany	**Allowed**. The health status and body weight are evaluated regularly. Fluid control must be scientifically justified and explained in protocols.
India	**Allowed**. By a minimum of 20 mL/kg/day (in PRLs). Body weight is measured regularly to ensure that animals are adequately hydrated.
Iran	**Allowed**. The health status and body weight are evaluated regularly. Fluid control must be scientifically justified and explained in protocols.
Japan	**Allowed**. The health status and body weight are evaluated regularly. Fluid control must be scientifically justified and explained in protocols.
Mexico	**Allowed**. The health status and body weight are evaluated regularly. Fluid control must be scientifically justified and explained in protocols.
Netherlands	**Allowed**. By an absolute minimum of 100 mL/day and a minimum average of 35 mg/kg (metabolic weight)/day over the last 3 days. Metabolic weight is weight in kilograms raised to the power of 0.75. It more accurately reflects the monkey's fluid requirements as heavier monkeys require proportionately less water than lighter monkeys; e.g. a 10 kg animal must, on average, receive a minimum of: $10^{0.75}$x 35 = 197 mL of fluid per day. Fluid intake, both received during training and supplemented in the cage, is monitored daily and logged in an electronic system accessible by researchers, caretakers and inspectors. During breaks in the training schedule of more than one day (e.g., weekends), the monkey receives a full water bottle of at least 700 mL, and animals over 15 kg receive an extra bottle. If the break is only one day, then the animal receives an amount of fluid equal to what it would typically receive during a training session. The animal receives a non-working period once every 9 weeks (on average over a year). During this period the animal is not trained and receives a full bottle each day (>700 mL). Follows a strict protocol.
Russia	**Allowed.** Only permitted under conditions of weight control and stability of working weight.
UK	**Allowed**. By a minimum of 20 mL/kg/day or a minimum of at least 3–6 h per 24 h. Require one day of ad libitum per week. Weekly, regular weighing of NHPs needed. Follows guidelines as per Prescott et al. 2010).
USA	**Allowed**. By a minimum of 20–22 mL/kg/day. Requires scientific justification and approval by the IACUC. USDA guidelines (*9 C.F.R. § 3.75 – 3.92*) require access to fluid at least twice a day. This requirement is often exempted on a protocol-by-protocol basis with scientific justification. Documentation and careful weighing and monitoring of the animals is required. Use of animals' preferred fluids in lieu of restriction is encouraged. Minimum amount of restriction necessary to perform tasks is also encouraged.
Section P	**Food control**
Belgium	**Not applied.**
Canada	**Allowed**, same as fluids.
China	**Allowed**.
France	**Allowed**. Animal welfare must be assured as assessed by the animal welfare body. Must weigh monkeys at least twice a week. Working weight should be stable. Post-experimental training food complement should be high protein food, and should be weighed to achieve the trade-off between motivation and minimal daily caloric intake.
Germany	**Allowed**. The health status and body weight are evaluated regularly. It should be scientifically justified and explained in protocols.
India	**Not applied.**
Iran	**Not applied**, but in special cases it is the same as fluid.
Japan	**Allowed**. The health status and body weight are evaluated regularly. It should be scientifically justified and explained in protocols.
Mexico	**Allowed**. The health status and body weight are evaluated regularly. It should be scientifically justified and explained in protocols.
Netherlands	**Not applied**, but European regulations would apply if done.
Russia	**Allowed**, when alternating experimental sessions (2–3 per week) with days when there is limited access to a variety of foods. No more than 15% weight loss allowed.
UK	**Allowed**, but follows guidelines in Prescott et al. 2010. If food is given at specific times (i.e. after experimental testing/training), then a minimum weighed amount of high calorific protein mash is required based on weight and age of the monkey. Must weigh NHPs at least every two weeks. Always have to be gaining or maintaining a stabilized weight, otherwise intervene if weight drops 10% from original.
USA	**Allowed**, same as fluids.
Section Q	**Capture**
Belgium	Use of pole-and-collar with appropriate habituation and training using positive reinforcement training (PRT).
Canada	Any handling or restraint technique must be safe for the animal and the handler and minimize stress.
China	Either pole-and-collar or, for trained monkeys, jump into a chair. Initial training involves encouragement with food, water, juice, and the monkey learns to trust the trainer.
France	Squeeze-back cages, nets, and pole-and-collar, based on PRT and clicker-training.
Germany	Restricted use of pole-and-collar; whenever possible monkeys should be trained to jump into their chairs.
India	Use of pole-and-collar (in PRLs).
Iran	Use of pole-and-collar. In some cases, monkeys are trained to jump into their chairs.
Japan	Squeeze-back cages, nets, and pole-and-collar. Training based on PRT. After training, manual guidance of the monkeys to the chair, using leash and protective equipment.
Mexico	Manual guidance on the monkeys to their chairs, using protective equipment.

(*continued on next page*)

Table 2 (*continued*)

Section Q	Capture
Netherlands	Trained monkeys come into their chairs. A leash is used for safety. On rare occasions, a pole-and-collar method may be necessary, but this is discouraged and avoided.
Russia	PRT to have monkeys go into a transport cage and then to a chair.
UK	Restricted use of pole-and-collar (i.e. it is not allowed as the only option in the UK). Use of PRT.
USA	As needed, use of pole-and-collar with appropriate habituation and training.
Section R	**Restraint**
Belgium	During the training periods animals are typically in the setup 5 days per week, head-fixed for 1–5/6 h per day (typical is 2–3 h, but monkeys are allowed to work as long as they wish). This holds for electrophysiology and neuroimaging.
Canada	Any handling or restraint technique should be introduced gradually through PRT to minimize stress for the animals.
China	Head-posting up to 4 h per day for neurophysiology, up to 2 h per day for neuroimaging.
France	Time limits on head-posting: up to 6 h (neurophysiology); up to 2–3 h (awake neuroimaging). Typically, 4–5 days. Monkeys cannot work more than 5 days in a row.
Germany	Head-fixing is possible up to 5–6 h maximum. Cannot work more than 5 days in a row.
India	Head-fixing is possible up to 4–5 h maximum.
Iran	Head-fixing is possible up to 6 h maximum in neurophysiology. Typically 4–5 days in a week.
Japan	Head-fixing typically 2–4 h in the monkey chair, 3–5 days in a week. Varies depending on individual experiments.
Mexico	By use of a training chair.
Netherlands	During the training periods, animals are typically in the setup 5 days per week, head-fixed for 1–4 h per day (typical is 2–3 h, but maximum is 4 h). This holds for both electrophysiology and neuroimaging.
Russia	Restriction of head mobility during the experiment for 2 h.
UK	Time limits on head-posting: up to 5 h (neurophysiology); up to 2–3 h (awake neuroimaging). Typical is 4–5 days per week; not allowed 6 days of max restraint in a row. Monkeys cannot work 7 days in a row.
USA	Scientific justification and approval by the IACUC required. Restraint up to 12 h (otherwise considered housing).
Section S	**Ongoing training**
Belgium	At least 24 h of continuing education initiatives per three years.
Canada	Personnel conducting training must be competent, with demonstrated expertise.
China	Once a year.
France	The GDR Biosimia (https://gdr-biosimia.com) focuses on the 3Rs and animal welfare. Expectation is to attend annual meetings on a regular basis. All participants in NHP research or care have to comply with the EU Directive 2010/63/EU (a minimum of 3 days training in 6 years). Animal welfare bodies reinforce regular attendance to training events in France and Europe.
Germany	At least 2–8 h of Continuing Professional Development (CPD) training per year, depending on the state. Veterinary associations require up to 25 h per year of specific continuing education from their veterinary specialists for laboratory animals/laboratory animal science (or *Fachtierarzt für Versuchstiere/Versuchstier*; *German Federal Veterinary Society*, *Bundestierärztekammer e.V.*, https://bundestieraerztekammer.de).
India	Personnel working with NHPs must attend an orientation program where all aspects of NHP training and handling are discussed.
Iran	PIs and new researchers require training. The institute reinforces regular attendance to training events at least once a year.
Japan	Lectures and e-learning (depending on the institute).
Mexico	N/A
Netherlands	Staff are trained internally and in collaboration with the national primate center.
Russia	N/A
UK	Each individual carrying out procedures with NHPs must attend standardized nationwide training courses, pass examinations, and hold a Home Office Personal License (PIL: which is a legally binding document). Internal training is also provided by experienced PILs, and veterinarians in the lab. Individual training records are inspected by certified training officers, veterinarians, welfare officers, and Home Office Inspectors (HOIs). Regular attendance at primate welfare meetings run by the UK National Centre for 3Rs is also expected.
USA	Individual PI initiated unless there are issues and the veterinarian, together with the IACUC, require additional training.
Section T	**Other?**
Belgium	N/A
Canada	N/A
China	Animals take turns in large play cages, the frequency of which depends on animal usage, but typically once every two weeks.
France	NHPs can be reused if retrospective evaluation of cumulative experimental severity is favorable in accordance with the EU Directive. Pre-determined humane endpoints are defined in the authorized project. This also applies to euthanasia. Animal welfare bodies discuss the issue and, along with the veterinarian, have the final say. All French governmental biomedical institutions using NHPs (i.e., CNRS, INSERM, CEA) are members of AAALAC.
Germany	N/A
India	Behavioral and neurophysiology experiments on NHPs are very limited in India and currently only performed at the Primate Research Lab (PRL), Indian Institute of Science (IISc). Therefore, for some of these questions, explicit guidelines are not available from CPCSEA. In such cases, we have followed the guidelines recommended by the funding agencies: DBT-Wellcome Trust India Alliance (who recommend the UK guidelines) and NIH (U.S. guidelines). Euthanasia: Every effort is made to rehabilitate, and in PRL, we have been able to rehabilitate most of the animals so far. Monkeys can be used again (to record from the other hemisphere if needed). The total duration is up to 5 years, including training, etc. Animal euthanasia is followed in situations as defined below: (i) When the animal is paralyzed and is not able to perform its natural functions or becomes incapable of independent locomotion, or can no longer perceive the environment in an intelligible manner; or (ii) If, during the course of an experimental procedure, the animal has been left with a recurring pain, wherein, the animal exhibits obvious signs of pain and suffering; or (iii) Where the non-termination of the life of the experimental animal will be life threatening to human beings or other animals. The veterinarian has the authority to euthanize the animal in consultation with at least one additional veterinarian if required, following diagnosis of an animal disease or injury. If possible, the veterinarian should discuss the situation with the PI to determine a course of action consistent with experimental goals.
Iran	Animals take turns in large play rooms in open space with sunshine. The duration of restriction is reduced by having in-cage training. Also use different flavors for liquid rewards to encourage monkeys to perform tasks without fluid control.
Japan	Humane endpoints dependent upon the institute.
Mexico	N/A
Netherlands	N/A
Russia	N/A
UK	Humane endpoints must be specifically defined for each authorized procedure that is carried out on a non-human primate.
USA	N/A

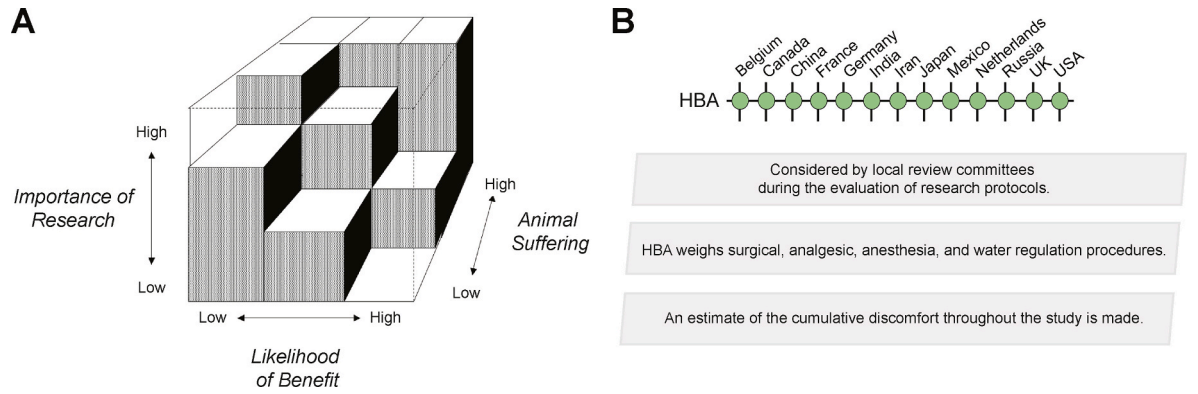

Fig. 2. Harm-Benefit Analysis (HBA) as a common moral imperative. (**A**) Bateson's cube used to capture the low-to-high probability of the three core factors assessed in the HBA: (1) Importance of Research, (2) Likelihood of Benefit, and (3) Animal Suffering (Bateson's cube. Adapted from *PLOS ONE*. doi.org/10.1371/journal.pone.0193758.g001). If research is of high importance with a certain likelihood of benefit, and minimal level of suffering, then it will fall into the hollow (unfilled) area of the figure, meaning research should proceed. Painful, less important research with lower likelihood of benefit will be categorized in the solid (filled) area, and should not proceed. Most research will not be clear-cut, but the guiding principle is 'hollow' should continue, 'solid' should not. (**B**) Overview summary of the Harm-Benefit Analysis (HBA) used for the approval of NHP protocols across the 13 countries included in this review.

experiments. Some may view that the harm to animals outweigh the benefits of conducting further NHP neuroscience experiments (e.g. Padrell et al., 2021); however, the HBA provides a measure for balancing potential harm with expected benefit (see Fig. 2a). When systematically applied, the HBA is a valuable tool for animal welfare review committees and regulators to weigh the ethics of animal experiments.

The HBA is highlighted in the *Principle of Expected Net Benefit* (DeGrazia and Beauchamp, 2019), in which the prospect of social benefit from a research study outweighs the expected costs and risks to human beings, and in another principle - *Sufficient Value to Justify Harm* (DeGrazia and Beauchamp, 2019), in which the prospect of a net benefit for human society from a research study is sufficiently valuable to justify expected harms to animal subjects. These social benefit principles may be used to help construct an evidence-based approach to the HBA. However, an often-overlooked issue relates to potential harms to human society if particular types of (NHP) research cannot be performed. The cost to society for *not* carrying out scientific research with animals should be factored into the harm-benefit assessment. For example, there may be an ethical cost to humans for doing nothing (e.g., in relation to developing genetically modified NHP models; Parker, 2020). Research with animals needs to be authorized and funded with the goal of improving the health and wellbeing of humans and animals.

In regards to the value of foundational research, the benefits of a project can have a singular focus on 'societal benefits,' but it is difficult to estimate, especially for fundamental (basic) research experiments. Foundational research projects often involve animal models and do not necessarily produce an (immediate) applied or translational benefit. However, applied or translational research builds heavily and uniquely on fundamental knowledge accumulated over decades. In other words, basic research produces knowledge that may lead to applied or translational benefits (e.g., Clements and Avery, 1998; Verkhratsky et al., 2006). Moreover, translational research is only possible by the foundation of prior and ongoing basic research. Given the nature of experimental research and the longer timeframe to identify successful outcomes, it can be difficult or near impossible to fully anticipate the likelihood of success and the overall value of the outcome for an individual experiment or research project (Niemi, 2019).

In addition, Niemi (2019) also highlights that the HBA approach does not incorporate the potential for refinements that benefit the animals or that alternative methodologies may emerge as the experimental research unfolds. For example, a protective primate head covering was recently designed and optimized to support wound management after cranial implant surgeries during the course of the experimental research work (Perry et al., 2021). Likewise, new implants have been designed that allow non-invasive alterations of the equipment attached to the implant (Blonde et al., 2018). These points, together with the public opinion on the societal benefits of animal research, constitute valuable perspectives to incorporate into the approval of each NHP research project.

All countries reviewed here currently apply, or are moving toward, the regulated judgment of the validity of NHP experiments through HBA (Fig. 2b; Table 1 Section F). A good example of HBA regulation is observed in Japan where, depending on the nature of the research being conducted and degree of pain, suffering, and distress experienced by the animals, experimental protocols are grouped into five categories. The Principal Investigator (PI) must fully understand which level of pain category applies to their proposed research when preparing an animal experiment protocol, and follow specific regulations relevant to the approved pain category in their experiments (www.jnss.org/en/animal_primates). With the USA animal welfare review committees, there is a discussion of the HBA, usually done for research protocols that are defined as USDA Category E, or for protocols in which pain is unrelieved by analgesia (Carbone, 2011). Guidelines for the UK HBA conducted during research project reviews have been made publicly available online (see Animals in Science Committee, 2020).

3. Identify common ground

It is not easy to compare regulations across borders given nuanced differences in ethical approaches and regulations. Here, an attempt has been made to highlight points where a consensus can be reached (see Fig. 1 and Tables 1 and 2). We note that any identified differences in ethics and regulations can reflect nation- or culture-specific viewpoints, and, if required, an evidence-based approach may be most appropriate to align any differences. Importantly, there is consensus on physical enrichment, placing limits on levels of pain, suffering, and distress, humane euthanasia, submitting proposed protocols for approval to ethics committees, obtaining project authorization, and allowing fluid or food control only under strict guidelines. There is also the encouragement of positive reinforcement training (PRT) in capture and training protocols (Prescott and Buchanan-Smith, 2003). Effective methods for implementing PRT, along with negative reinforcement training protocols, have been published (Mason et al., 2019).

There are some similarities in minimum requirements, particularly evident within EU countries, which makes sense as they are all bound by EU regulations (see EU Directive 2010/63/EU). The UK regulations have been aligned with the EU Directive since 2012, and these remain for the most part, but there are a few differences (e.g., for re-use of the same

NHPs in successive projects). In the UK, NHP research project approval (license) is carried out for a specific project involving a defined number of animals, and further re-use of an animal for a different project, although possible, is rare and it is extremely difficult to seek approval. In the EU, re-use of an animal on successive projects can be permitted by the LC, depending on the level of harm that occurred in prior projects, and as long as it is scientifically justified. In contrast, for China, Japan, Mexico and the USA, animals can be re-used on successive research projects, although the re-use of an animal must be scientifically justified and authorized (see Tables 1–2; https://prime-re.github.io/hardware_and_protocols/global_collab.html).

Another similarity noted across countries is a minimum weaning age for macaques and marmosets (Table 2 Sections F-G). Further, in all countries surveyed, except in India and the USA, the use of wild-caught NHPs for neuroscience research purposes is banned. Although the use of wild-caught NHPs in neuroscience research is uncommon at academic institutions in the USA, concerns regarding illegal trade (www.nytimes.com/2022/11/16/us/cambodia-monkey-smuggling-ring.html) highlight at least two important considerations. First, the USA can and should increase its investment in domestic breeding colonies, especially the National Primate Research Centers (see also www.fool.com/investing/2022/12/18/americas-primate-shortage-hinders-medical-research/). Second, the extensive expertise in breeding, behavior, and care of NHPs can be leveraged for partnerships with experts in conservation biology, locally and across the globe, to ensure the vitality and sustainability of wild populations in habitat countries. For all countries, laboratory facilities are routinely inspected to ensure compliance with all requirements for high-quality NHP care and experiments (see Table 2 Section B for country-specific details).

Regulations and permissible NHP accommodation differs among countries. For instance, single housing is strictly regulated, but allowed in exceptional circumstances in the majority of countries reviewed (see EU Directive 2010/63/EU amended by Regulation (EU) 2019/1010 (European Parliament and the Council of the European Union, 2010, 2019), NC3Rs, nc3rs.org.uk; and NIH/OLAW guidelines on NHP care). In Japan and Russia, it is generally allowed, while in Belgium, single housing can only be used for quarantine or health reasons, or exceptionally and temporarily for experimental reasons. The minimum cage size varies from country to country (Table 2 Sections H–K). In India, Iran, Japan, and the USA, the cage size depends on the animal's weight. The minimum cage volume for adult macaque monkeys is specified for the UK and countries within the EU (1.8 m^3), Russia (0.9 × 0.9 × 0.8 m^3), Mexico (1.1 m^3) and China (1.0 × 0.9 × 0.7 m^3). It is worth noting that in practice most institutions across our survey exceed the minimum stated limits for their NHP housing requirements to provide suitable space with ample room for species-specific interactions and behaviors. Also, when determining the ideal space for NHP group interactions, a key consideration is to balance space and resources to promote good animal welfare (Buchanan-Smith et al., 2004). In response to an increase in international collaboration, the Japanese Neuroscience Society updated its own Guidelines for the Care and Use of NHPs in Neuroscience Research (https://www.jnss.org/en/animal_primates). These guidelines also include the goal of introducing cages that can accommodate social groups by 2030. Additional guidelines for terrestrial animals, such as macaques, may be sought from evidence-based examples in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011).

Double-tiered housing units are used in multiple places for pair-housed animals or as playground areas (Table 2 Section L). In most countries solid, as opposed to grid flooring, is the preferred choice. Solid flooring allows the NHPs to more readily engage in species-specific behaviors, e.g., foraging amongst the substrate on the floor for scattered food, seeds and grains. In other cases, there are no specific regulations or short-term exceptions for grid flooring (Table 2 Section M).

Globally, there are specific recommendations for physical enrichment (e.g. NIH guidelines, NC3Rs guidelines, EU Directive 2010/63/EU). One of the recommendations is that animals are able to control the environment according to their own independent choices. Additionally, introducing novelty, variability, choice, and manipulation are recommended. Ideally, the implementation of changes and improvements that are authorized at the institutional level can ensure that NHP accommodation is enriched, safe, comfortable, and affords opportunities for NHP physical and social interactions, and that these norms are compatible across collaborating institutes. Reporting housing conditions in scientific publications is an additional way to enhance rigor and reproducibility in neuroscience (Pomerantz et al., 2022).

Other commonalities we observed among the reviewed countries include defined limits for the amount of pain, suffering, and distress that an animal may experience in experimental protocols that are approved. Also, any form of controlled fluid intake is a regulated procedure managed under ethical authority, during which the health status and body weight of the animal are closely and regularly monitored, often on a daily basis. Fluid control (also referred to as fluid scheduling) refers to control over the total volume of fluid or time it is available to an individual animal on a daily basis. Fluid control means that fluid (typically water) is provided to experimental animals using controlled access rather than being ad libitum in the home cage. It is an experimental method used for motivational purposes of animals to ensure consistent behavioral performance (Prescott et al., 2010), especially when the experimental tasks they are required to complete are cognitively demanding (e.g., Prescott et al., 2012). During fluid control, animals on experimental schedules receive fluid rewards during testing sessions when they are completing experimental tasks (the volume of fluid is recorded), then back in the home enclosure further fluids may be provided, i.e., either according to a minimum daily volume (e.g., 20 mL/kg/24 h) based on the individual animal's body weight, or according to a minimum amount of scheduled time, e.g., typically for at least 6 h per 24 h.

Similarly, food control (also referred to as food scheduling) is also an experimental method used to motivate the animals to perform consistently in cognitively demanding tasks. Neuroscientists in some of the contributing countries do not use food control. Like fluid control, food control is a regulated procedure that is managed under ethical authority and the animal's weight is monitored regularly, typically weekly or more often. Food control involves scheduling the daily intake of food that each animal consumes instead of providing food ad libitum in the home cage. Similar to fluid control, the total number of food or fluid rewards consumed in the experimental task is recorded, and then afterwards the animal is given its daily weighed portion of high calorific food. Even on food control, animals also receive seeds and grains as a forage mix in the home caging and also receive other low calorific food (e.g. pieces of vegetable, popcorn) at other scheduled times throughout the day (for recommendations see Prescott et al., 2010). Details of fluid and food control methods are required to be stipulated during the publication of experimental results, in accordance with the guidelines for Animal Research: Reporting In Vivo Experiments (ARRIVE; Sert et al., 2020a Sert et al., 2020b).

While commonalities exist, we observed that there are also regulatory differences amongst the countries (summarized in Fig. 1, see also Tables 1–2 for details). These differences may be better navigated by working towards a common understanding of the individual nation's regulations and standards. A global framework should incorporate common standards and local diversities. Further, a fundamental understanding of these regulations and standards in NHP neuroscience research may be critical for validating results obtained across multinational collaborations, especially when the scientific questions involve aspects of an animal's physical and social environment. To navigate this space with regard to international collaborations, being aware of the common understanding and where it diverges requires sharing of information.

The capacity for finding common ground is contingent upon the resources and availability of an accessible database. In addition to digital

data (e.g., neuroimaging scans), NHP scientists may share and therefore send abroad tissue samples that would be best analyzed in a collaborating laboratory. The shipment of tissue samples from NHPs is regulated by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES; cites.org/eng/disc/text.php). It was created originally to prevent fraudulent and illegal movements of endangered species trophies. The CITES offers museums (e.g., natural history museums) the opportunity to share specimens based on their recognized CITES accreditation, with limited administrative steps to make an exchange possible. However, research institutions are not included in this opportunity, and each specimen being sent abroad (e.g., from the USA or UK to the EU, or from Canada to the USA) requires the collaborators to apply for a CITES export permit and a CITES import permit (border crossings within the EU do not require such permits because of shared trade regulations). This procedure is often lengthy and makes immediate shipment for urgent sample processing impossible. We propose that the simplified procedure offered to museum collections should be extended to research institutions that could then apply to receive a similar CITES accreditation. Striving for similar standards and protocols is fundamental for the reproducibility of neuroscientific findings. The interplay of ethics, animal welfare and local committee oversight on the reproducibility of animal studies is discussed further by Pritt and Hammer (2017).

4. Cooperate with scientists on a global scale

Scientists recognize the importance of working with colleagues across labs and institutions, and across nations to avoid redundancy and share expertise for added value. An exciting aspect of cooperative scientific research is the potential for neuroscientists across the globe to actively participate and share their expertise, while also learning from others. Some great examples of such endeavors are Brainhacks (Craddock et al., 2016; Gau et al., 2021), Brainweb (https://brain-web.github.io/), and NeuroMatch (van Viegen et al., 2020). Global collaborations incorporating NHP neuroscience should support scientific discovery and ensure the best possible animal welfare approaches are obtained - these dual objectives can complement each other.

With global collaboration, cooperation is required between teams and institutions to achieve trans-national agreements. Independent formal support at the trans-national level (in the form of a multinational NHP neuroscience set of guiding principles) would be particularly welcome. Aside from the great ordeal of acquiring funding, another factor to consider is the applicability of approved NHP neuroscientific research and ethical protocols that are acceptable in one country compared to another. Multinational studies have to consider the animal welfare guidelines in each country, where lead researchers, PIs, and the institutions in each country address differences in the guidelines. As such, collaborating members would have to conform to the same animal welfare standards to ensure uniformity across studies. In this case, the most rigorous standards do not equate to being the strictest set of regulatory constraints, but rather to an expansion of conditions that ensure scientifically-grounded improvements in NHP animal welfare. We must also recognize that ethical and animal welfare review boards may need to formalize international collaborative studies without becoming bureaucratic and overly complex. Further, this process must adhere to openness to ensure all parties understand the levels of approval shared between countries, the responsibilities of each individual involved, and what level of flexibility is necessary or even possible.

Finally, on a related level, cooperation between NHP colleagues, breeding facilities, funding agencies, institutions, and policy makers is essential to continue to ensure the global supply of NHPs and conservation of these precious animals in their native habitats. The future supply of NHPs for biomedical research is raised by Janssen and colleagues (Janssen et al., 2023). The breeding of animals for scientific purposes, and even the development of transgenic models (Feng et al., 2020), relies upon specialized breeding facilities and a nation's supply of NHPs. The global supply shortage has been prominently featured in many forms of media (e.g., Subbaraman, 2021).

5. Share and contribute to information resources

The accessibility and willingness to cooperate in the sharing of information is a recurring theme in considering (inter)national collaborations and regulations. Not many countries can perform the full spectrum of possible experiments and collect neuroscience data. Thus, it is important to maximize the use of accumulated data worldwide. Recently, we have seen the fast development of open databases for sharing animal data, and experienced the benefits of rapid data sharing during the Covid-19 pandemic caused by the SARS-CoV-2 virus (Weir et al., 2022). The SARS-CoV-2 genome was made available across several platforms (e.g., GISAID, gisaid.org; INSDC, insdc.org) and updated from all around the world in real-time, answering the call for data re-distribution and openness (Van Noorden, 2021). There are many advantages gained from open database promotion.

Data sharing has been promoted by the growth in open access models for scientific publication and information dissemination (European Commission, 2017; Van Noorden, 2021; Weir et al., 2022). In recent years, the NHP neuroscience community has started to move towards the sharing of data and resources (Milham et al., 2020, 2022). The PRIME-RE (https://prime-re.github.io) platform was built around this philosophy (Messinger et al., 2021). Such collaborations have been shown to lead to further sharing and improvement, and, where relevant and possible, standardization of underlying experimental and welfare protocols (Basso et al., 2021; Milham et al., 2020). Further, hematological, physiological, and behavioral data sharing is essential to better inform long-term health and wellbeing assessments of NHPs involved in neuroscience experiments (e.g. Wegener et al., 2021). Certainly, when researchers share experimental data, they effectively increase the sample size of their data, which, in the case of NHP neuroimaging studies, will mitigate some issues of rigor, reproducibility and validity (Botvinik-Nezer et al., 2020). However, sharing data alone does not necessarily imply that an increase in the number of animal subjects is the only way to enlarge the available dataset, as considerations of reproducibility can also include increasing the number of experimental sessions. For example, in neurophysiological studies with NHPs, two animals are commonly the smallest number that can be studied. For NHP work, this is justified because the sample size can include the number of data points collected (e.g., from a recording site) across multiple sessions. Depending on the power for a given effect size, two or more animals may be needed to show that results in one could generalize to other animals. Furthermore, neuroscience case studies in NHPs can provide valuable insights to understanding the brain and its function in primates (e.g., Bridge et al., 2019; Lear et al., 2022).

The sharing of scientific methodology in published works is a staple of research, and many researchers may follow standards of information sharing, such as the ARRIVE guidelines (Sert et al., 2020a). Data sharing in this way is critical for reproducibility, especially because science is said to be facing reproducibility issues (Baker, 2016; Begley and Ioannidis, 2015; Botvinik-Nezer et al., 2020). Although the information provided as part of reporting animal research by the ARRIVE guidelines can help, it may not provide all information needed for collaboration or address every form of international collaboration that may be needed. Thus, another key ingredient is to share (and develop) the resources and approaches for mining and synthesizing such information provided in published papers. This approach began with national information sharing (Mitchell et al., 2021), and was extended here to include additional countries. The information can include how different institutions/nations conduct their ethical assessment and regulatory frameworks, including whether and how the required HBA is conducted during the development of protocols for NHP research (Basso et al., 2021; Gray et al., 2016). Thus, we encourage the efforts of neuroscientists from other nations involved in NHP research to share more about

their regulatory processes and welfare standards, so that we may obtain a more comprehensive understanding about the commonalities and differences across this global scientific field.

Currently, there are several identified reasons common to scientific groups that stop development of openness and sharing of resources through common databases. Core barriers to data sharing include: the lack of any standardized procedure for appropriate attribution, which can be detrimental to the career prospects of (junior) researchers who collected the precious data; competitive pressure amongst scientists and between nations; the necessity to continually secure further funding; and restrictions on dataset sharing by research organizations and societies (Matthews et al., 2020). The true challenge will be to establish an international culture of openness and collaborative science that will allow such shared resources to thrive and, in return, benefit the animals, the research community, and the broader public as a whole.

The present article tries to raise awareness about each nation's welfare standards regarding NHP biomedical (neuroscience) research. This is particularly useful when managing data from several different countries. Differences and similarities in welfare regulations and standards at the national level may help draw additional evidence from meta-studies to inform the most appropriate common standards. NHP research papers could include additional details about their welfare standards (e.g. housing conditions; Pomerantz et al., 2022), in addition to referring to a guiding principle, law, or regulation. Thus, the maintained shared resource introduced in this paper can serve as a basis for facilitating collaborations across labs while a standard set of regulations are being developed.

6. Communicate with the public and policy makers

Trusted relationships are a key element in sustaining successful working relations (Reina and Reina, 2016). Importantly, being aware of, understanding, and communicating about the commonalities (and differences) across animal research regulations in countries where collaborative research is becoming particularly crucial for the success of such endeavors. Thus, communication and engagement between scientists is critical. However, equally important are science communication and engagement with policy makers and the public (Bubela et al., 2009; MacArthur Clark et al., 2019; Mitchell et al., 2021). Engaging with the public and policy makers effectively helps to improve the public's understanding of the benefits of animal research. This is essential as ongoing support from policy makers and the public is required to ensure the continuation of biomedical research involving animal models (MacArthur Clark et al., 2019). Training on public engagement and describing the importance of research for funding agencies, regulators, and administrators can prove beneficial when embraced by scientists (e.g. Mendez et al., 2022).

Openness (in the form of sharing knowledge, methodologies and resources) in animal research is also important. Many openness initiatives to help better inform the public about primate neuroscience research have been made publicly available (e.g., Cambridge University, UK, www.cam.ac.uk/research/research-at-cambridge/animal-research; DPZ, German Primate Center, Germany, www.dpz.eu/en/about-us/profile/mission.html; Emory University, USA, www.yerkes.emory.edu; KU Leuven, Belgium, gbiomed.kuleuven.be/english/corefacilities/research-involving-laboratory-animals/animal-welfare-1/primates; and the U.S. Animal Research Openness (USARO) Initiative, www.usaro.org).

An understanding of the global norms may be especially relevant and could aid communication when the discussed research involves multiple countries that might employ varied frameworks and regulatory standards (Novinger, 2001; Samovar et al., 2014). Certainly, global efforts are necessary to facilitate education of the public and policy makers worldwide, so that the importance of research involving NHPs is realized. Research institutions and relevant governmental bodies (e.g., health and education ministries) should undoubtedly provide ways to support this outreach and their animal researchers (Bennett, 2017). Further, communicating about the value and importance of animal research must be identified and recognized as a fundamental part of supporting animal research programs, with the help of the institutions and governments, rather than something to be done outside of institutional obligations (Mitchell et al., 2021). Such commitment to auxiliary roles should be taken into consideration for institutional and board-level performance evaluations.

7. Conclusion

International collaborations are accompanied by a number of fundamental challenges bound to regulations. Here, we acknowledge several of these challenges in the context of NHP neuroscience research and offer solutions towards a future of accessible, ethical and scientific global collaboration. While formulated in the specific context of neuroscience, these solutions may easily be extended to all fields of research using non-human primates, including immunology and vaccine development, gene therapy, regenerative and precision medicine, comparative psychology and cognitive science. This paper outlines five key ingredients for harmonizing and communicating about animal research ethics and regulations, in order to support successful international collaborations amongst NHP neuroscience researchers (see Fig. 3).

We discussed potential ways to facilitate international NHP collaborations and aggregated information from 13 countries that support NHP biomedical science (in particular experimental neuroscience), and can be used as a resource for NHP researchers, funding agencies, regulators, policy makers, and the public to examine the regulations and standards for NHP research in each of these countries. The value of NHP research, and the return back to science and society, is directly related to the quality of data and the welfare of the animals. Both can be enhanced by collaborations without national borders. Based on our comparative analysis of animal research regulations in these 13 countries and the multiple similarities observed in ethical regulations and welfare standards, we can conclude that there is good potential for a global NHP framework to support future collaborations. These similarities include a regulated process of animal welfare review and oversight, rigorous assessments of the proposed research, including using a HBA, and defined limits of discomfort. The identification of trans-national concordance here provides a basis for finding common ground (Fig. 1).

Setting up a global framework in which to collaborate with this special animal model provides many important and unique opportunities to add further value and benefits with advances in our understanding of neuroscience research and improvements to animal welfare. One of the challenges, however, of working across international labs is the acquisition of research funding. There is a clear gap and urgent need for funding agencies to support global-international neuroscience research involving NHPs, while at the same time incorporating any declarations that must be accounted for when managing the regulatory systems of different countries. Importantly, a global framework needs to facilitate research and funding opportunities addressing timely scientific needs, rather than the oversight and regulatory burden that can often impede this research by being too slow and cumbersome (Homberg et al., 2021).

To this end, how might the institutions, funding agencies, scientists, regulators, and policy makers develop mutually agreed upon means for considering an international set of standards for NHP research? Does it provide regulation that is acceptable for all? Many, but not all, countries adhere to the NIH (OLAW) standard. However, over a decade ago, the World Organization for Animal Health (WOAH) issued the recommendation of common standards that its member countries adhere to for the "Use of Animals in Research and Education." This recommendation could be used as the basis of discussion for the adoption of an international declaration to guide and support responsible biomedical research with NHPs. In addition, to consider swift action on the promotion of global collaborations, countries falling out of consensus may turn to this

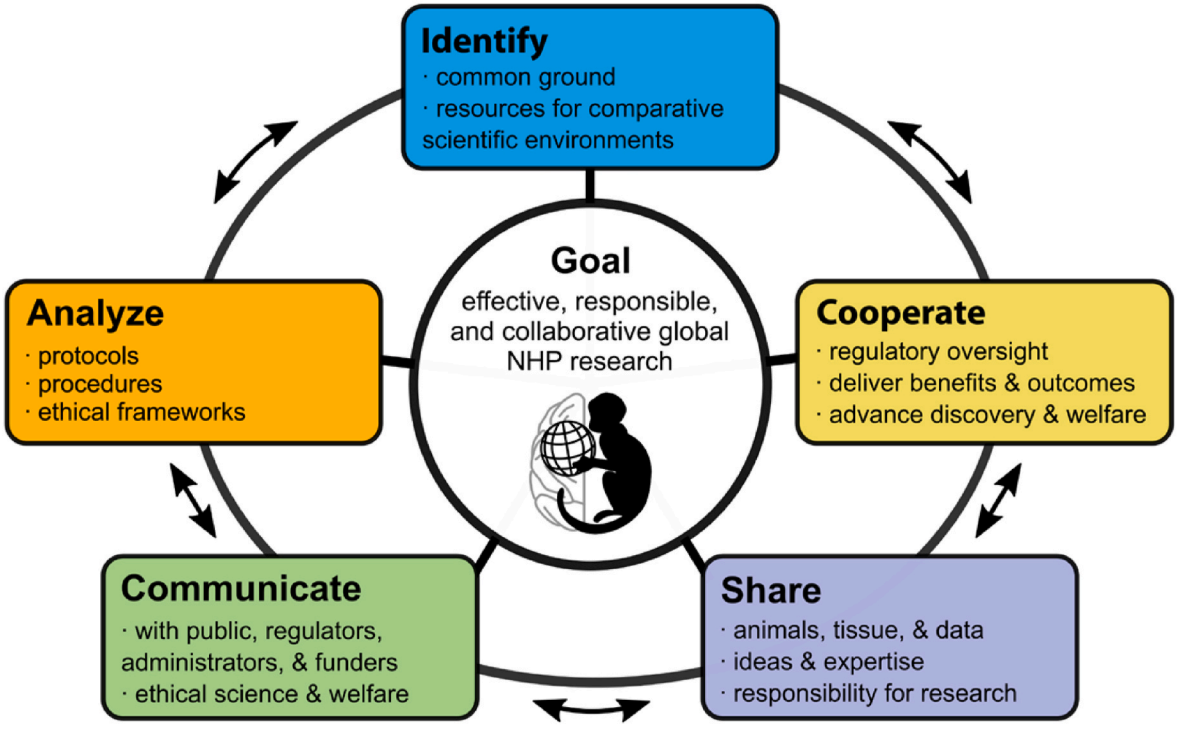

Fig. 3. Five key ingredients interact to support the goal of effective, responsible and collaborative global non-human primate (NHP) research. Through the analysis of the regulations as well as the identification of common ground and understanding of cultural differences, we may achieve timely regulatory assessment and support for international collaborations in NHP biomedical research. Through cooperation we can synergize strategies to attain our overall aims of advancing scientific knowledge. The sharing of knowledge and resources coupled with communication is a critical step towards reaching the central goal. As with any recipe, the key ingredients influence the end result and, in our case, interact to establish the multifaceted goal of effective, responsible and collaborative global NHP research.

set of international standards on regulation and ethics for reference, along with the country-specific regulations.

CRediT authorship contribution statement

Renée Hartig: Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Resources, Visualization, Writing – original draft, Writing – review & editing. **P. Christiaan Klink:** Data curation, Investigation, Methodology, Visualization, Resources, Writing – original draft, Writing – review & editing. **Zlata Polyakova:** Data curation, Investigation, Visualization, Resources, Writing – original draft, Writing – review & editing. **Mohammad-Reza A. Dehaqani:** Data curation, Resources, Writing – original draft, Writing – review & editing. **Igor Bondar:** Data curation, Visualization, Resources, Writing – review & editing. **Hugo Merchant:** Data curation, Resources, Writing – review & editing. **Wim Vanduffel:** Data curation, Resources, Writing – review & editing. **Anna Wang Roe:** Data curation, Resources, Writing – review & editing. **Atsushi Nambu:** Data curation, Resources, Writing – review & editing. **M. Thirumala:** Data curation, Resources, Writing – review & editing. **Amir Shmuel:** Data curation, Resources, Writing – review & editing. **Vishal Kapoor:** Resources, Writing – original draft, Writing – review & editing. **Katalin M. Gothard:** Investigation, Writing – review & editing. **Henry C. Evrard:** Resources, Writing – original draft, Writing – review & editing. **Michele A. Basso:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing. **Chris Petkov:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Anna S. Mitchell:** Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The information resource has been made publicly available online here: https://prime-re.github.io/hardware_and_protocols/global_collab.html.

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Appendix A. Supplementary data

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