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Abstract:	This document is an ethics deliverable created following the 2nd ethics assessment. It responds to Requirement 5 concerning the way animal data is treated.		
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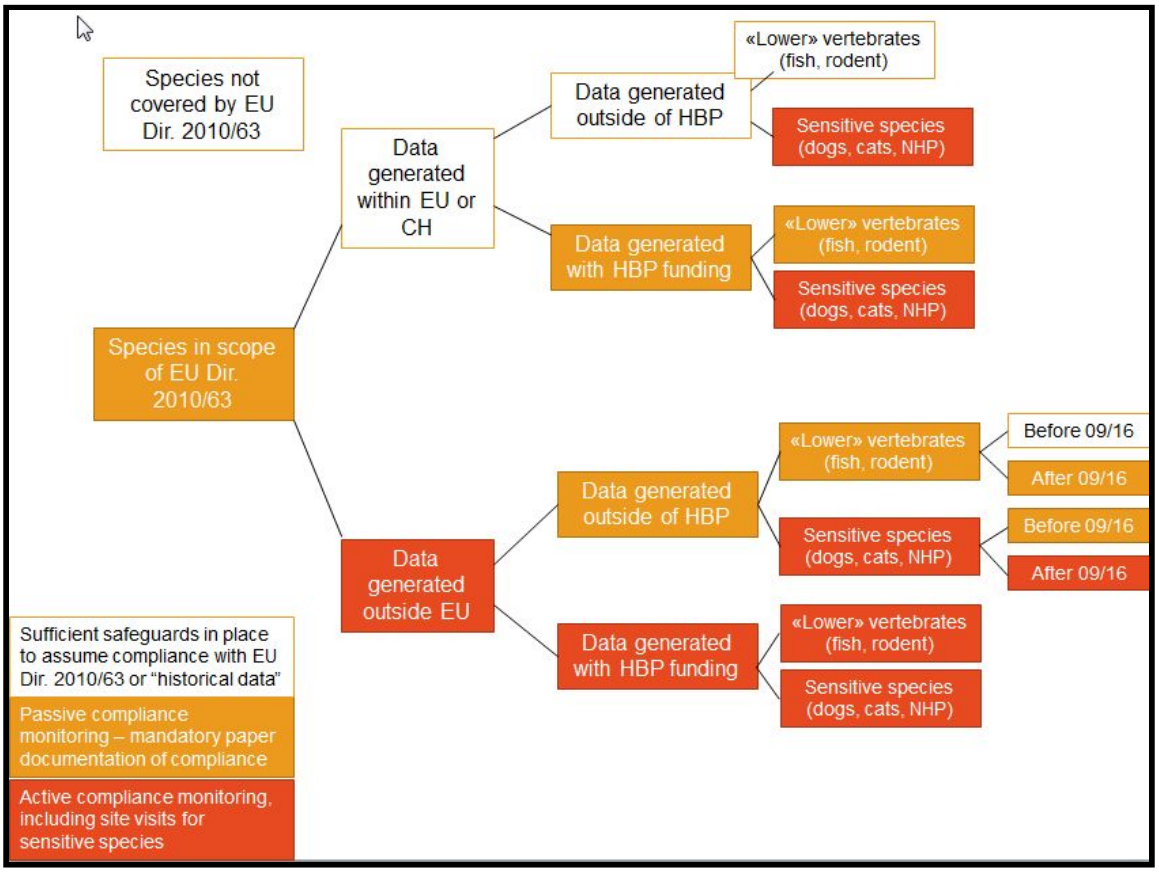
1. Executive Summary

This document explains how animal data generated in third countries is to be treated in the HBP. Based on the HBP compliance management principles and European regulation and guidance, following conversations with EC ethics reviewers and numerous experts on animal ethics, the HBP will distinguish between animal data generated by the HBP and animal data originating outside the HBP.

Depending on the type of data, the species involved and the date of data collection different levels of ethical oversight and compliance procedures will apply.



The justification of this approach and the detail of the ethics compliance requirements for the different cases are explained in detail in the document.

2. Introduction

Following the second Ethics Assessment of the HBP SGA1 (Ares(2016)2676349), a deliverable was inserted in the DoA that requested the following ethics requirement:

> "Regarding the use of animal data from third countries, the applicants must outline how the consortium will ensure that such data have been obtained in compliance with Directive 2010/63/EU.".

This deliverable addresses the issues.

3. Background

The use of animals and data derived from animal studies within the HBP is an issue that requires utmost ethical attention. European citizens and policy makers as well as the concerned scientific community rightfully demand that the 3R principles – replace, reduce, refine – are prioritized in all scientific efforts. The main efforts of the HBP are undertaken within European countries. Notably, Europe has on a global level the highest animal welfare standards, laid down in the European legislation Directive 2010/63 which governs animal research in all EU Member States, as well as in non-EU states such as Switzerland.

The HBP is a hugely complex project which strives to accelerate the fields of neuroscience, computing and brain-related medicine. An integral part of the scientific work in the project covers animal research and animal data. The EC finances research on animals notably in Subproject 1 (Mouse Brain Organization) and Subproject 3 (Cognitive Architecture). In other Subprojects, notably SP5 (Neuroinformatics Platform) data derived from animal research which has not been funded directly through the HBP is also to be incorporated. In both cases the animal studies may have been conducted within or outside the EU. The fact that animal research outside of Europe may contribute to the HBP rightfully raises concerns.

Thus, a key task of ethical attention and compliance in the project must be to ensure that all animal use funded by the HBP is fully in line with European laws and regulations. At no point in time should HBP funding be granted to animal laboratories outside EU which have housing and care standards that are not in accordance with EU provisions.

The question whether this rigorous approach should also apply to animal data generated

without HBP's financial support is more difficult to answer. Key findings may be published in peer-reviewed top journals without key information on the conditions under which the animals were kept and used. Such data may be historical (i.e. results from studies concluded recently or even a long time ago) or current. While such data may be highly relevant for the success of the HBP, the concerns that the project harvests "fruits of the forbidden tree" are relevant and have to be taken seriously.

This document sets out and discusses the principles on which animal data produced in third countries outside the EU is being addressed in the HBP.

4. HBP Compliance Procedures - Re, Animal Data

Animal research and data are currently ethical issues addressed through the HBP's standard compliance processes. The principles according to which compliance is managed are set out in the Compliance Management SOP[1] and details are explained in the Compliance Management Instructions[2]. The SOP is an official HBP policy document that was adopted by the Board of Directors during the Ramp-up Phase. The Instructions represent a working document that details how work is undertaken.

All ethical issues that are related to compliance are dealt with as follows:

I. The PI (typically every task leader) is sent the Self-Assessment Survey, which is based on the H2020 Ethics Self-Assessment[3]. This happened during the Ramp-Up phase, at the beginning of the the SGA1 period, and also in preparation for the SGA2 period. As part of the Self-Assessment Survey, PIs are clearly informed that they must not start any research activity requiring approvals unless they have the approvals in place.

II. The Survey clearly helps flag where a PIs' research has H2020 ethical issues and where ethical approvals are going to have to be further provided. In such cases PIs are sent a second survey, the "Research Ethics Document Review Survey". This is used to collect further information on the approvals that are required.

III. In addition to filling in the second survey, PIs must also submit the actual approvals. This must be for the duration of their research within HBP, including renewals where applicable.

IV. These approvals are then internally reviewed by members with relevant expertise within the Ethics Management team.

V. All of these activities are logged in an overview spreadsheet which is the starting point for the HBP "Ethics Registry". Links to all approvals and documents which are stored in the secure Tresorit system are included in the Registry.

These principles apply to all H2020 research activities which include human and animal research as well as data governance.

Additionally it is reasonable to assume that all PIs and researchers working with animals in HBP are adhering to the 3Rs principles - reducing, refining and replacing - in animal experimentation.

It is also reasonable to assume that they are:

- Appropriately qualified and have undergone training in LAS (Laboratory Animal Science),
- Have extensive knowledge and experience in handling of the laboratory animals they work with, and
- Have taken reasonable steps to avoid redundancy (a 4th R) in the experiments eg Use of databases.

Furthermore, regarding these points and in particular to the last point, it is reasonable to assume IRB reviewers themselves will have these checks in mind when they are reviewing proposals and will assess whether PIs have undertaken an appropriate systematic review of the literature (to avoid redundancy and possible duplication) before they will grant a proposal ethical approval.

5. Animal Data as a Third Country Issue in HBP

HBP will make use of third country animal data. HBP is a data integration project that aims to make data available to HBP researchers but also to other potential user communities. This can be done via the Neuroinformatics Platform where data may be registered which was not produced and is not held by any HBP partners but which may be used within the HBP or via the HBP. This is the case that raises the most significant questions.

There are two extreme positions that could be pursued:

1. *Requirement of full adherence of all animal data to EU requirements:*

   Adopting this maximum position implies the ethical superiority of the European approach to animal research which is a potentially problematic position in itself. However, this position would be fully on the safe side from the ethics perspective, as it would mean that there is evidence of the ethical acceptability of all data. While this would be desirable from the perspective of ethics, it would be very problematic from a scientific perspective. Other countries may have reasonable and ethically defensible ethical positions that nevertheless do not fully match European requirements. Such data would be ruled out by default. The bar for using data within the HBP could therefore be so high that sharing data would cease to be of interest to scientists outside the HBP who want to use third country animal data. The HBP would therefore find it more difficult to engage relevant scientific communities and thus to achieve its own goals.

2. *Failure to take into account the ethics of data production:*
The other extreme would be to ignore ethics when using external data. This would simplify processes greatly but would open the door to bypass ethical regulations and thereby potentially render them void. This is probably what the ethics reviewers refer to as the "fruit of the forbidden tree".

It would appear that both of these extreme positions are not suitable to the HBP and to an EU-funded project. The ethical principles of the EU and the intention to protect animals to the highest degree while still facilitating scientific research should guide the way to practical solutions.

In March 2017 the Ethics Management Team held a Joint Workshop with the EAB and Ethical Rapporteurs on "Animal Data from third Countries", in Bristol UK[4]. This included presentations which provided the basis for: (i) An understanding of the ethical and political issues associated with the use of animals in the HBP (ii) A vision of the relevance of the 3Rs in the neuroscience context, and (iii) Insights into practical experiences in the handling of 3Rs at one of the biggest vivaria in Europe (The Karolinska Institutet). This was followed by a discussion on the Animal Data SOP to be applicable for HBP, and how to respond to the EC Ethics Review comments on animal research and data.

As reasonable measures in research collaboration involving third countries it was felt that it was fair and appropriate to ask that the HBP PIs to be responsible for ensuring that the collaborators in third countries follow ethical rules in line with EU guidelines. For example a formal agreement should be in place with the laboratory in the third country regarding the ethical guidelines to be followed. Documentation should also be provided assuring that the collaborator in the third country laboratory institution adheres to internationally accepted ethical regulations and follow the 3Rs principle.

6. Animal Data in the HBP Platforms and the Way Forward

Animal data, as all other data, will form a key component of the Platforms in particular the Neuroinformatics platform. This platform is being rethought and the Data Planning and Implementation Team is working on a sustainable approach to dealing with data. The outcomes of this work will have a significant bearing on the practices of registering, curating and making available data, including third country animal data. Ethics Management is part of this process and sees third country animal data as one example of a broader set of questions that are discussed under the heading of "data governance" that will need to be tackled in parallel. The work concerning data governance will lead to the development of a number of interlacing policies, some of which will concern third country animal data. This is an ongoing process.

To move forward and to provide a practical basis and solution for the development of data governance, the Ethics Management team proposes the following ideas and principles.

These will be fed into the data governance development processes which are expected to lead to a comprehensive set of policies governing relevant aspects of data governance, including the question of how and under which circumstances to register data with SP5 or other parts of the HBP.

For practical purposes we distinguish between the following types of data:

I. Data sourced from animal studies commissioned by/financed through the HBP
II: Data re-used from animal studies conducted outside of the scope of HBP/without funding from HBP

For the first category we agree to only use data/study results from centers which comply with EU regulation 2010/63. A supplementary documentation must be provided upon submitting such proposals to the HBP.

For the second category we agree to introduce a grandfather provision, i.e. all data generated before September 1st, 2016 shall not be affected by new provisions but treated as ethical re-use of animal-derived data. Not using the data which might help to gain important scientific insights may arguably be ethically more problematic compared to using such data.

For data generated post September 1st, 2016 (the date this deliverable was first submitted to the EC) we will use only raw data sourced from facilities which have proven compliance with the US ILAR Guide for the Care and Use of Laboratory Animals[5]. However, this does not apply to the the use of summary/abstracted data gathered from publicly available bioinformatics databases, where the provenance of the individual data components cannot feasibly be tracked. The ILAR guide provide internationally highly accepted set of standards for the housing, care and treatment of laboratory animals which is in the case of rodents delivering a globally acceptable standard. Such compliance can be substantiated by an AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) accreditation or by a publication in an international tier 1 peer reviewed journal that endorse the ARRIVE guidelines[6].

Furthermore ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines have been developed to "improve the reporting of research using animals – maximising information published and minimising unnecessary studies[7]. They promote the aims of animal protection while at the same time strengthening the scientific quality of publications. It is therefore proposed to explore with HBP scientists whether the HBP should adopt these guidelines internally as a reporting standard required of all HBP-funded publications covering animal data.

The ethical status of animal data (and other ethically relevant data) should form part of

the metadata collected during the process of registering data with the HBP. This may include the following:

a) Simple, understandable classification system on the ethics of animal data such that the uploader can indicate to which category his/her data belongs (e.g. A1: data generated according to Directive 2010/63/EU; A2: data generated according to ARRIVE guidelines; etc.)

b) A way for the data uploader to indicate that this information is sound and correct, including a contact address in case some user of the data has questions related to the ethics of data generation.

As a way to deal with animal data in HBP a classification system of animal data has been proposed and is provided in Figure 1 (see below).

There are three classification systems:

I. No ethical/compliance review required (white boxes in diagram)

A small group of animal data is considered unproblematic as one can assume that existing safeguards are sufficient to grant compliance with EU Dir. 2010/63. This applies to data generated in the EU or CH which use "lower species" such as fish and rodents. If such data have been generated without HBP funding the geographical location of the research entails the EU law must have been respected in the set-up and approval of the research.

Also "historical" ex-EU data of lower vertebrates such as fish and rodents should qualify for use in the HBP. If such data have been generated and published in peer-reviewed journals the effort to retrospectively trace the housing and care standards applied may be disproportionately high and the fact that such data is already part of the scientific discourse should be respected.

II: Passive ethical/compliance review required (yellow boxes in diagram)

In many cases the generation or use of animal data will require passive ethical/ compliance review, i.e. it will be mandatory for HBP researchers to document compliance of their animal research with EU laws and regulations. For animal data that are used in the HBP but not originating from research funded by HBP the passive compliance monitoring will require similar written documentation.

Passive review is only acceptable for lower species such as fish or rodents.

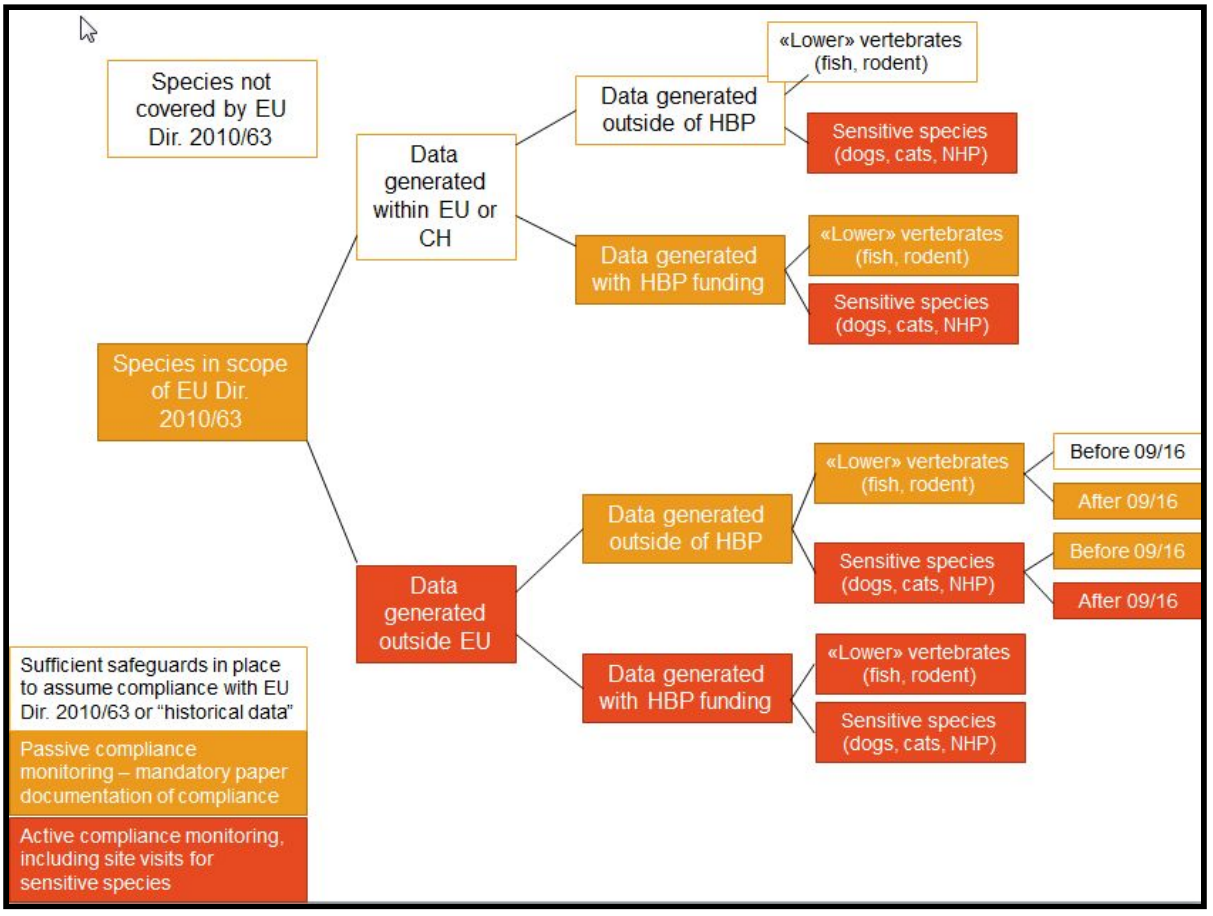


Figure 1. Classification of animal data in the HBP

III: Active ethical/compliance review (red boxes in diagram)

Some use of animals or animal data are so sensitive that it will require active review, i.e. documented interviews with the investigators and in all cases where non-human primates are concerned, site visits at the laboratories. Site visits can also include non EU sites doing work on rodents and funded by HBP.

7. Conclusions

Animal data from third countries has been recognised as a potential area for ethical concerns. The HBP strives to follow the highest EU standards regarding animal data: applying the 3Rs, following Directive 2010/63/EU, together with advice from EC sources

and Union Reference Laboratories. HBP is committed to finding measures to ensure the research from third countries is done following acceptable ethical standards including proper use of experimental animals, minimizing discomfort and distress and consistent with sound scientific practice.

Finding the right balance between the scientific interests and the ethical need to protect animals is not straightforward. It require detailed discussion between different stakeholders, notably the HBP researchers undertaking animal research and using third country animal data, the Ethics Management team, the Ethics Advisory Board, the EC's ethics reviewers and external stakeholders.

Following the principles outlined here will help the HBP ensure compliance and high ethical status of animal research. It will also provide incentives for animal researchers in other countries to improve their rules and standards.

This deliverable should be understood as a direct response to the 2nd Ethics Assessment report in which the Ethics Management team formulates its proposed approach to the use of third party animal data. Ethics Management is not a decision-making body of the HBP. The eventual policy will need to be developed in consultation with the SPs and will take into account other aspects of data governance. The decision to adopt and implement a policy rests with the governance bodies (SIB, DIR, SB).

As the data governance work is under way, ethics reviewers are welcome to comment on these proposals and feed their suggestions into the broader discussion of data governance.

Appendix 1: HBP Policies on Redundancy in Animal Research

Within the HBP the following are considered to be utmost reasonable measures which help ensure that no animals are used in experiments without proper justification:

1. The Project Lifecycle App (PLA) developed in the context of the DPIT work and reconstitution of the Neuroinformatics Platform (NIP). This tool allows for the mapping of interdependencies of all components in the HBP. Data sets are one of these components. The consequence of using this tool is that there is high visibility of all components and their use and relevance in the overall HBP can be easily ascertained. The concern that animal research is undertaken without consideration of its role in the HBP is therefore no longer relevant.
2. All animal research in the HBP is subject to the normal ethics review and approval procedures, notably the EU Directive 2010/63/EU and its national implementations. According to the resulting processes, animal research can only be approved if there is a sufficient scientific rationale behind it. All animal research undertaken in the HBP therefore has been checked prior to commencement. To avoid redundancy, it is incumbent upon the Researcher to do a systematic review of the appropriate literature before embarking on a proposed study. Research without a proper scientific justification would not be approved.

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