



VETBIONET

Veterinary Biocontained facility Network for excellence in animal infectiology research and experimentation

Deliverable D4.2

Analysis of ethical issues in BSL3/BSL3+ animal infectious disease research Report

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Table of contents

Summary	3
1 Introduction.....	5
2 Mapping Key Ethical Issues	7
3 Ethical Analysis of Animal Technologies	12
4 8Es Approach to Infectious Disease.....	19
5 Summary	24
6 References	26
7 Annexes	28
8 Acknowledgements	29

Summary

Objectives:

The aim of this report is to map some of the ethical issues that are relevant to research work conducted within the field of animal infectious disease. There is recognition that reflection on issues should not only be focused on the key issues of animal research ethics such as the application of the 3Rs, experimental design and the processes of ethical review, but it is important to widen the scope of reflection to issues, taking into account issues that relate to ethics in animal infectious disease research which include framing questions, issues of inclusion, dissemination and responsible innovation. As such, aspects of the wider discussion of ethics in research and the role of frameworks and tools are also reflected upon.

Rationale and Approach:

The remit and rationale of this report is to draw on insights and tools from the literature and the input of the members of the network to map and highlight some of the ethical issues raised by animal infectious disease research conducted at BSL3/BSL3+ facilities. An initial scoping exercise was conducted and this was complimented by series of mapping activities and analysis of issues conducted through dialogues at the VetBioNet events. Initial mapping work was conducted at VetBioNet annual meetings (2018/2019). Further sessions and activities have occurred at VetBioNet training events and other meetings, such as Annual Meetings in 2020, this has supported further identification and development of approaches. Other activities such as training events, have created spaces to open up and highlight key issues. A survey was also conducted in 2021 to draw out specific issues on culture of care and 3Rs and support the identification of key aspects and activities that will be important to consider as part of the sustainability activities of the VetBioNet Network.

Outcomes

The scoping and outlining of the issues highlight the importance of mapping key ethical issues through the lens of Principles, Practice and Policies. Principles refers to guiding principles such as the development of 3Rs approaches. Practice refers to how aspects are operationalised, such as through the review processes of Animal Welfare Bodies and tools to support decision-making related to Humane Endpoints in animal experimentation. Policies refer to the role of regulation and the embedding of ethical

principles such as the 3Rs consistently across institutions in Europe and how harmonisation can support good practice. Alongside this lens there is also a recognition that a number of tools and frameworks can support reflective analysis. For the development of new technologies and research programmes, frameworks such as the Ethical Matrix approach and an 8Es approach can support researchers as they characterise, analyse and respond to the ethical aspects raised by their work. The development and provision of training that focuses on ethics by design and 3Rs also support reflective practices for those involved in delivering the training as well as receiving the training. These approaches and frameworks should be helpful in supporting the long-term activities of the VetBioNet animal infectious disease research network.

This deliverable (*Deliverable D4.2*) represents the first version of this report and has been informed by the work of the Network and is informing the work of the network going forward. However, this report will be revised at the end of the project as issues from the networks activities and final data is published from the research activities of the network.

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1 Introduction

The aim of this report is to highlight some of the ethical issues that are relevant to research work conducted within the field of animal infectious disease and demonstrate some ethical frameworks that can be used to support this field of research.

Animal Infectious Disease Research and ethical issues

Animal infectious disease research is an important area of research investment at a national level and within EU programmes. This area of research has been prioritised in order to categorise and tackle a wide range of endemic and novel disease outbreaks which can have significant human and animal health implications as well as have significant economic impact on the farming sector. The importance of conducting research in animal infectious disease, particularly zoonotic diseases, has been particularly highlighted by the coronavirus (COVID-19) pandemic, which has had an enormous impact on health and wellbeing as well as significant economic implications. Before this, significant animal infectious disease outbreaks across Europe have been mapped for diseases such as Bovine Spongiform Encephalopathy, Bluetongue and Foot and Mouth Disease to name but a few. All of these types of outbreak have required dedicated and coordinated research efforts.

Alongside these types of endemic diseases and the current focus on coronavirus research, there is concern about the emergence and transmission of new animal infectious diseases within EU. With concerns about coronavirus and the emergence of zoonotic diseases, such as the two prominent influenzas; avian influenza virus (e.g. H5N1) and swine influenza virus (e.g. H1N1), there is what some have claimed to be an ethical imperative to invest in this area of research, in terms of professionals, facilities and technology innovation. For the farming and animal industries there is also recent EU outbreaks of Schmallenberg virus and African Nile Virus to contend with, both of which have significant animal health implications.

There is clearly a need to invest and develop a robust research area in animal infectious disease and within this research work there is an obligation to have principles, tools and approaches available to support the identification and analysis of key ethical issues raised by this research. This includes a focus on the use of animal

in experimentation, the development of novel animal biotechnology, as well as issues of biosecurity and biosafety.

In parallel to processes embedded in the work conducted across the VetBioNet network, both individual researchers and research centres are increasingly exploring approaches and opportunities to embed wider responsible research innovation approaches. Not only is it important to highlight some of the key aspects that have ethical significance such as the application of the 3Rs and issues of a culture of care, but it is also important to identify frameworks and tools that can be used by researchers when dealing with a wide range of issues. A further important aspect is the need to find ways to open up discussions of issues across this network and the wider research community. Approaches that can be used and ways in which this can be done include:

- Creating ethical tools that can facilitate analysis and discussion
- Identifying spaces and environments which encourage open discussion of issues
- Identifying mechanisms that support good practice, such as ethical review processes
- Providing network learning spaces where researchers can share good practice approaches with each other and the wider community, for example through annual meetings and workshops

Although there needs to be a clear focus on the important issues of animal research ethics such as the application of the 3Rs, experimental design and the processes of ethical review, it is also essential to place these specific issues in a broader context identifying wider issues that can be taken into account when planning animal infectious disease research. This includes examining framing questions, issues of inclusion, dissemination and responsible innovation.

Therefore, to facilitate an important exchange of approaches and mapping of issues VetBioNet researchers have participated in a number of sessions and activities that facilitated discussion of the ethical issues raised by their work in the network and on animal infectious diseases. These discussions have also been complemented by other specific activities with the network and defined tasks (that have led to distinct deliverables, such as on biosecurity and on training).

Approach

The remit and rationale of this work is to draw on insights and tools from the literature and the input of the members of the network to map ethical issues raised by animal infectious disease research conducted at BSL3/BSL3+ facilities. An initial scoping exercise was conducted and this was complimented by a series of mapping activities and analysis of the issues through dialogues conducted at the VetBioNet events. Initial mapping work was conducted at annual meetings (2018/2019). A further session and activities have occurred at VetBioNet meetings, such as Annual Meetings in 2019 and 2020, this has supported further identification and development of approaches. Other activities such as training events, have created spaces to open up and highlight key issues. A survey was also conducted in 2021 to draw out specific issues and support the identification of key aspects and activities that can contribute to the work across the VetBioNet Network that will be important for the longer-term ambitions of the Network.

From these processes several key aspects emerged. Firstly the value of looking at the key ethical issues raised across animal infectious disease through the lens of principles, practice and policy aspects. In addition to this, the need to develop and provide frameworks and tools which can support the mapping of issues and assist those who wish to conduct an ethical analysis. It is hoped that the development of a new framework will help to support wider ethical analysis and can help researchers manage ethical issues that are important in research programme design. This is intended to support the future work of VetBioNet and aid the longer term sustainability of the network, as an effective research collaboration and space for good practice exchange.

2 Mapping Key Ethical Issues

Introduction

This section highlights some of the key issues that are raised by animal infectious disease research that have and are being taken forward in specific activities and work plans across the VetBioNet programme. A number of key themes have been initially identified and these are set out below. For some of these specific issues, deliverables

have or are being produced to focus on topics more specifically and for other aspects it has been valuable to share current approaches and good practice. These issues include: (a) considering how experiments are conducted and how alternatives can be used; (b) considering the animal welfare of laboratory animals and how procedures can be refined such as humane endpoints, (c) considering the impact and role of EU legislation and how this has been translated at a national level, (d) considering biosafety / biosecurity criteria and compliance, (e) reviewing and reflecting on the role of ethics committees in defining and promoting acceptable and good practice. All of these issues have been directly taken forward in specific work within Workpackage 4 or other Workpackages (such as the issues of biosafety / biosecurity criteria). One way to address these issues is to examine them through a structure of three key aspects that are important to consider in animal infectious disease research, specifically principles, practice and policies. Each of these are important aspects that help researchers consider the underpinning principles of practice as well as reflect on the boundaries set by regulation or institutional policies. Examples of these are discussed below in terms of the work that has been conducted in the VetBioNet.

Principles.

One of the key principles that underpins animal infectious disease research practise is the 3Rs approach (Russell and Burch, 1959). The 3Rs concept (Replacement, Reduction and Refinement) was proposed by the UK scientists Bill Russell and Rex Burch in 1959. These underpinning principles are applied to set out a more humane approach to research. The process of replacement focuses on finding alternatives to animal use by using human-based or non-sentient material. The principle of reduction focuses on examining the number of sentient animals needed to conduct an experiment and finding ways to reduce the number of animals used. Finally, the principle of refinement focuses on the welfare of the animals that are justified as needed in any experiment, so that levels of animal distress are kept to an absolute minimum. The application of these principles has been the focus of the VetBioNet Guidance on Implementation of the 3Rs (Deliverable 4.4). This report highlights the importance of these principles as underpinning ethical principles in animal infectious disease research. Hobson-West (2009) claimed the 3Rs approach could be characterized as a scientific concept (related to experimental design and validity of methods) or a political concept (helping to present this work to publics and promote a

consensus approach for research that might be deemed to be controversial) and also as an ethical approach. The use of the 3Rs approach in the research field of animal infectious disease appears to focus on the ethical presentation of this concept, with acknowledgement to the scientific argument, and this significantly underpins the Networks work as (set out in the deliverable 4.4) *“given the potentially severe nature of many of the animal models for the study of infectious diseases and sometimes limitations on housing, husbandry and care imposed by high biocontainment, finding innovate ways to apply the 3Rs principles to infectious disease research is essential to ensure good practice and high ethical standards are maintained”*.

Practice

In terms of practice and building on underpinning principles, the work of VetBioNet has focused on which practices can support an ethical approach. This has included highlighting new approaches to specific questions that have been raised as important, such as defining humane endpoints. Issues of defining and managing ethically sound humane endpoints is a key issue for those conducting infectious disease research work (Hendriksen, 2009; Franco NH et al 2012). New approaches are highlighted in meeting exchanges and workshops activities as raising awareness and sharing knowledge is an important aspect when discussing the ethical issues raised by this area of research. An example of this awareness raising and knowledge exchange is highlighted by Humane Endpoint decision-support tool (see table 1).

Table 1 – The Endpoint Matrix: Decision-Support tool (Ashall and Millar, 2015)

	DEFINE What is it?	DETERMINE How does it apply to the experiment?	DETECT Who, how, and when?
SCIENTIFIC ENDPOINT	The criteria which will be used to indicate that the experimental objective has been reached.	What specific and minimum (e.g. $P < 0.05$) data is required? At what point will no further data be required?	Who will set the scientific endpoint? (e.g. PI or responsible investigator). How and when will data collection be

		How does this affect expected suffering and cost benefit justification?	<p>monitored and how will this be reported?</p> <p>Who will determine when the scientific endpoint has been reached?</p> <p>What alternative actions are available?</p>
JUSTIFIABLE ENDPOINT	The maximum level of suffering which can be justified by the expected benefits of the experiment.	<p>Ethical review should perform a cost / benefit analysis of studies which are expected to cause suffering.</p> <p>The animal indicators of the limit of justifiable suffering should be determined before the study commences.</p> <p>How will any suffering be avoided, alleviated and/or minimised?</p>	<p>Who is trained to recognise expected suffering?</p> <p>How will they recognise and report the justifiable endpoint?</p> <p>Who will decide to end the experiment?</p> <p>What action should be taken and what alternatives are available?</p>
UNINTENTIONAL ENDPOINT	Unpredicted suffering which is not related to the experimental aims or is beyond what was expected.	General indicators of pain and/or suffering must be monitored in addition to expected specific signs.	<p>Who is trained to detect unpredicted pain and suffering?</p> <p>Who will determine whether the experiment should continue? (e.g.</p>

			designated vet or animal welfare officer) What action should be taken?
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Alongside this work, focusing on awareness and knowledge exchange, there has been work conducted on specific practice-oriented activities such as the role and remit of Animal Welfare Bodies. This work is important to highlight to researchers in the field, how effective ethical review can be supported through the functions of their local Animal Welfare Bodies and Ethics Committees. This examination of practice was conducted through the delivery of a report examining Animal Welfare and Ethics Committees Best Practice (Deliverable 4.5). This work, alongside other activities, provides practical recommendations on how the functions of Ethics Committees can be addressed by BSL3 facilities. This work also highlights useful resources and tools to support practice. Of course, this is an ongoing conversation of processes and practice and further work is needed to support researchers. This aspect is an important one for the ongoing network.

Policy

Finally, it is important to contemplate policy issues and this aspect has also been considered across the Network through a number of activities including work looking at “Implementation of the 3Rs and EU Animal Experimentation Directive” (Deliverable 4.4). The principles that are important in underpinning animal infectious research have more recently be directly embedded in legislation, explicitly written into Directive 2010/63/EU. Mapping and characterizing the development and role of legislation is an important aspect. Researchers are directly affected by regulations but can also input straight into some aspects of the policy-making process, so it is important to be aware of policies and policy initiatives. As such some of the work on the ethical aspects of animal infectious disease research has focused on mapping the current regulatory landscape and a series of national profiles have been produced to support researchers individually as they navigate their own regulatory landscape or as they seek to collaborate across national boundaries. Policy aspects should not only be seen as regulations, but also wider policies and initiatives that can support the research, such

as training policies and initiatives. As such VetBioNet has also developed and delivered a number of 3Rs and Experimental Design Training Schools and a Summer Training School. These activities have also been delivered in partnership with 3Rs organisations (Ethics, 3Rs and Experimental Design Training in association with FELASA). These are also important network activities that can support harmonization across EU research institutes.

3 Ethical Analysis of Animal Technologies

One of the challenges of mapping and reviewing the ethical issues raised by an area of research is identifying an approach or method that can support this analysis. A tool that was developed at the University of Nottingham (Mepham 2000) has been used to map the ethical issues raised by development of new research methods and biotechnologies is the Ethical Matrix approach. This approach has been discussed within the Network at meetings in 2017 / 2018 and provides a useful structuring tool for mapping ethical issues. The approach, and a mapping example use for this research, is set out in this section. Before discussing the application of the Ethical Matrix to animal infectious disease research, the background of the tool and an example of the generic form of the tool is first presented.

The Ethical Matrix tool was first developed by a team at the University of Nottingham, it was first presented for the analysis of animal biotechnologies by Mepham (2000). The tool has been further developed by a range of research group across Europe and North America with groups in Norway taking forward the framework for the analysis of biotechnologies and food-related issues (Kaiser and Forsberg, 2001).

The Ethical Matrix approach is based on a principlist approach that uses a framework of three core ethical principles that are derived from an approach first proposed by Beauchamp and Childress (1979). The ethical principles of wellbeing, respect for autonomy, and justice are applied to set of interest groups that are deemed to have ethical standing. It is claimed that this approach provides a common, universally applicable approach to mapping the ethical issues raised by the development or application of an animal biotechnology. This approach is also a comparative method so that any proposed technology is compared to the status quo, with any potential

impacts that may occur from the use of the new technology are mapped and assessed against non-use. Using the tool therefore results in a map of potential trade-offs. The value of this tool is that it is able to map a range of issues and make the ethical issues at stake more transparent. The Ethical Matrix does not provide ‘an answer’ to the question of whether approaches, research plans or biotechnologies should be used but makes the value-based conflicts more transparent and therefore aids decision-making. Finally, any analysis, ethical judgements are made by attempting to achieve a reflective equilibrium. This entails users conducting specific assessments (on the basis of evidence, experience, uncertainty and reflection). Therefore, this approach requires additional specification and balancing as a way of identifying and addressing the key ethical issues at stake and any conflicts across the principles. Justification of this process is important, for decisions affecting public policy processes that can be supported by ethical analysis and any judgements need to be rational, comprehensive and transparent.

Table 2: Generic Ethical Matrix (Millar and Mepham, 2001)

Generic Ethical Matrix <i>(Translation of the ethical principles for the corresponding interest group)</i>			
	WELLBEING	AUTONOMY	FAIRNESS
PRODUCERS (e.g. Farmer)	Satisfactory income and working conditions	Managerial freedom	Equitable IPR conditions, trading and market systems
CONSUMERS (including affected citizens)	Food safety and quality of life	Informed democratic choice	Affordability and access to food
ANIMAL / TREATED ORGANISM (e.g. Dairy Cow)	Animal welfare	Behavioural Freedom	Intrinsic value

BIOTA <i>(‘Environment ‘ in some cases)</i>	Conservation and Protection	Biodiversity	Sustainability
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This framework has been used to assess a number of animal uses and animal biotechnologies, including for farm animal disease genomics (Millar et al, 2007), dog breeding (England and Millar, 2008) and the use of bovine growth hormone in dairy cattle (Mephram et al., 2006).

The Ethical Matrix can be used in a number of ways. (i) It can be used as a tool for mapping key ethical issues raised by the use of a new technology or method (e.g. a biotechnology, new farming method, food production system, new policy, etc). This would involve a qualitative approach, setting out written arguments for each of the cells for each interest group (e.g. animal wellbeing, autonomy and justice).

It can be used as an approach (ii), by a Committee, to map out key issues, conducting an ethical analysis and then inform and make transparent the process of decision-making conduct by that Committee (a qualitative approach). (iii) it can be used as a tool to support decision-making using a scoring system that attempts to allocate a ‘score’ to each cell and then aids the ranking or balancing of the ethical issues (a quantitative approach).

Finally (iv) it can be used as an approach to support dialogue and reflection. With this approach individuals come together, such as a diverse group of stakeholders, to discuss the ethical issues raised by a new technology or method. This approach can help identify different evidence that can support an ethical analysis and identify different views on which issues and evidence are significant. All of these approaches are relevant to the work of VetBioNet. However, the use of the Ethical Matrix as a mapping tool (i) will be presented below.

When using this approach to map the ethical issues raised by Animal Infectious Disease Research the following interest groups were identified (Table 3 sets out these interest groups and specification):

- Animals use in research

- Production Animals
- Researchers
- Farming Industry
- Society
- Environment

Table 3: Ethical Matrix specification for Animal Infectious Disease Research

Ethical Matrix for Animal Infectious Disease Research			
	WELLBEING	AUTONOMY	FAIRNESS
Animals in Research	Animal welfare	Behavioural Freedom	Intrinsic value
Production Animals	Animal welfare	Behavioural Freedom	Intrinsic value
Researchers	Satisfactory income and working conditions	Professional Freedom	Equitable working conditions and IPR opportunities
Farming Industry	Satisfactory income and working conditions	Managerial freedom	Equitable conditions and trading systems
Society	Safety, protection and social harmony	Informed democratic choice	Affordability and access to food

The ethical principles (wellbeing, autonomy, fairness) are then specified for these defined interest groups, e.g. Wellbeing of the Treated Animal is specified as an assessment of ‘Animal Welfare’. It is important that the abstract ethical principles are

specified to make them more concrete for the analysis of the case in hand. Specification is a process of translating the principles to give them action guiding capacity while still being true to the original commitment of the ethical principle. This analysis has been done in the extend table below which sets out key issues for Animal Infectious Disease Research Considerations. This table (Table 4) informs the wider work of the Network and has been taken forward in various forms through training, workshop dialogue, specific initiatives to map regulatory issues.

Table 4: Ethical Matrix for Animal Infectious Disease Research: Making issues

Ethical Matrix for Animal Infectious Disease Research			
	WELLBEING	AUTONOMY	FAIRNESS
Animals in Research	<ul style="list-style-type: none"> • Clear and high welfare standards for animals involved in experimentation • Consideration of the way animals are sourced (e.g. how and if animals should be taken from the farm to containment facilities) • For challenges test clear clinical endpoints and management of the animals • Focus on how all aspects of experiments can be refined and approaches to share this information • Review and refining of the nature of containment • For research that has the potential to cause animal suffering further work to define criteria for experimentation 	<ul style="list-style-type: none"> • Striving to determine better ways of confinement that balances the challenges of ensuring biosecurity of the experiment against the behavioural needs of the animal • Review of minimal needs of the research animal in terms of enrichment, how can enrichment and bedding provision be ensured • Does any adverse effect from the research environment which impacts the animal behavioural repertoire also affect the animal's health status and the outcomes of the experiment • Do we have enough information on how differences species react to and respond to containment? 	<ul style="list-style-type: none"> • In terms of justice, what ways are there to replace the use of large animals • Review the choice of species, are there assumptions about species choice or are some species 'less favoured' • Could pilot studies reduce numbers yet be scientifically valid. • Focus on the individual animal in group experiments so care is for the individual as well as the group • Important to clearly define the aim and outcome of the research so that animals are not unfairly use in speculative research
Production Animals	<ul style="list-style-type: none"> • Rapid responses to disease outbreaks can reduce animal suffering and unnecessary animal culling • Does the outcomes of this research results in controls on animals that affect their wellbeing • Does this research work contribute to greater use of intensive farming systems and increased animal welfare risks • Reducing disease load can have a positive 	<ul style="list-style-type: none"> • Outcomes from animal infectious disease research can result in changes to animal containment and housing which can have positive and negative impacts • Management of the farming system can result from this work that limits animal interaction and increase isolation which could have negative impacts 	<ul style="list-style-type: none"> • Does work on infectious disease further instrumentalise farm animals, by developing treatments vaccines for animal farming systems that have poor environment that increase disease risk and poor welfare standards

	<p>impact on animal wellbeing and reduce individual and overall animal suffering</p>		
Farming Industry	<ul style="list-style-type: none"> Technologies developed from this work can have clear positive impacts on farm incomes and working conditions Disease outbreaks can be sudden and unpredictable have significant impacts on farmers wellbeing, therefore rapid develop of testing and treatment approaches are key Rapid responses to animal infectious disease research can notably positively affect farmers wellbeing Work to test efficacy of vaccines and treatment measures support farmers wellbeing 	<ul style="list-style-type: none"> Supporting the definition of safety criteria and control criteria from a scientific perspective, making the evidence clear, can help farmers decision-making when decisions are often influenced many factors and stakeholders Connecting this research work directly to farmers and finding ways to include farmers in setting research prioritise can support their autonomy as a community 	<ul style="list-style-type: none"> Should farmers be involved in early testing of some of the vaccines or disease control approaches, would this be far treatment Researchers can support policy-making and the establishment of fair and transparent legislation in disease testing, reporting and control. Involvement in Public-private partnerships may support greater innovation and more efficient rollout of testing and treatment to farmers
Researchers	<ul style="list-style-type: none"> Researcher wellbeing is linked to doing 'good science' which is conducted according to clear standards and is responding to important research questions Institutional support for good practice and how research can collaborate is important for research wellbeing Clear safety and protection standards when working with infectious diseases. Clear safety and biosecurity standards Ensuring high standards and clear justification of 	<ul style="list-style-type: none"> Supporting staff decision-making through research team consultation Recognition that the ability to conduct work is affected by funding and funding can be very limited Importance of having support within an institution For those professions working in an institution that conducts animal experiments there can be restrictions on what can be discussed, how can this be better managed Great reflection on the who makes the ethical 'decision' to conduct an experiment and how can researchers input to this 	<ul style="list-style-type: none"> Important to have clear process so that all staff are treated fair, in terms of access to resources and opportunities Changing institutions or moving to new countries can require new training requirements, important that equivalent training and skills are recognised so unnecessary repetition of training or licences is not required Standards across processes can be more transparent such as AWB review processes

	<p>use for animal use so that researchers have every confidence in decision-making and standards</p> <ul style="list-style-type: none"> Appreciation of the expertise and experience of staff and what it means to work in challenging environments 	<p>and how do these choices affect others</p> <ul style="list-style-type: none"> Academic drivers and research impact criteria can sometimes affect choices which are not for the better and may affect research ability to act on farmers' needs 	<ul style="list-style-type: none"> Opportunities to benefit for innovation through personal or institutional IPR Some researchers face public challenges and direct action due to the work they are involved with or the institutions they work for, how can these researchers be fairly supported
Society	<ul style="list-style-type: none"> Clear societal need to identify, monitor and address animal infectious disease Tackling animal disease in farmed animals can reduce food safety risks and improve the quality of food products Conducting research on highly infectious zoonotic disease can present significant biosecurity risk from misuse of the research or from accidental release 	<ul style="list-style-type: none"> Finding ways to support engagement in research and research priority setting Full and open disclosure of the work conducted and transparency is the animal research that is conducted Open access dissemination of research methods and outcomes Details of how research is conducted in emergency settings and how this supports government responses to outbreaks 	<ul style="list-style-type: none"> Clear indications of what research is being conducted and how it supports society as a whole and different sectors of society Justification of research spending and the value of the work in combating important infectious diseases that have an impact on animal and human wellbeing and the wider economy
Environment	<ul style="list-style-type: none"> Environmental impacts from the direct activities of the research facilities Outcomes of the research may affect positively and negatively the use of some treatments such as antibiotic use Local biosafety risks that relate to potential accidental releases Disposal of waste set by EU regulations 	<ul style="list-style-type: none"> Will the outcomes of this research result in changes to farming systems that may affect biodiversity 	<ul style="list-style-type: none"> Environment Impact of the research units in terms of GHG emissions and non-renewable energy use. Due to the needs for strict biosafety protocols, significant use of single-use plastic and plastic waste Could increasing environmental controls increase the chance of this type of research moving to other regions

4 8Es Approach to Infectious Disease

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N°731014

One aspect that can be challenging when planning animal infectious disease research and considering ethical issues, is to map the issues in a holistic way. One approach that may help research consider the wide range of ethical issues in an all encompassing way is the 8Es approach. This approach aims to encourage reflection on the (Ethical) Validity of Research Projects and how these can be assessed at eight levels, i.e. it is an approach to ask a wide range of relevant questions of scientific research and the application of any knowledge produced from this research.

The 8Es approach involves consideration of the:

- (1) Empirical,
- (2) Experimental,
- (3) Epistemology,
- (4) Effects,
- (5) Evidence,
- (6) Empowerment,
- (7) Engagement,
- (8) Ethical

This approach attempts to bring together the many aspects that need to be considered when developing a research project or programme. The aim is to see the interactive aspects of the empirical through the ethical with the ethical encompassing all aspects rather than seeing these aspects as separate, as can sometimes be the case in research planning. This interconnectivity is highlighted by Diagram 1.

Diagram 1 – The 8E approach



The 8Es approach involves consideration of the: (1) Empirical, (2) Experimental, (3) Epistemology, (4) Effects (5) Evidence, (6) Empowerment, (7) Engagement and (8) Ethical levels

Level 1 - Empirical Level

This level focuses on the data that will be produce and asks questions related to the research work at the level of the data.

For example, how will you ensure data integrity? Who owns the data? How will the data be managed? Where will the data be stored and for how long? Will the data be open access, if yes, when and under what conditions? If the research data will be protected, by whom and under what conditions will the data be protected? Has a data management plan been prepared?

Level 2 - Experimental Level

This level focuses on the experiment and how this will be designed and asks questions related to the experimental aspects of the research work.

For example, how have you decided on your experimental design? What is your statistical approach? Does the research team have the skills to conduct this work? Are you using a hypothesis? What equipment is needed and are clear standards set for the experimental process, such as calibration requirements? How are you ensuring sound experimental standards? Are approvals needed for the experiments, such as review by an institutional ethics review committee or a statutory body?

Level 3 - Epistemology Level

This level focuses on the epistemology aspects of the research work and asks questions related to the knowledge produced.

For example, are there any assumptions built into this research work about the nature of the knowledge produced? Are there any elements of bias that may affect the experiment? Can the data be presented or analysed in different ways that may affect the interpretation of results? Could there be any challenges to the knowledge produced from this work?

Level 4 - Effects Level

This level focuses on effects of the research, both directly and indirectly, and asks questions related to the outcomes of the research work.

For example, what impacts may result from the research work in terms of economic, social and environmental impacts? Are there any biosecurity or biosafety issues raised? Will the results from this work affect any key stakeholders, such as farmers or consumers? How are any potential impacts being characterised or assessed, and by whom and when has or will this be done?

Level 5 - Evidence Level

This level focuses on the use of the research outcomes as evidence in professional and policy decision-making and asks questions related to how the outcomes of the research may be used.

For example, how is this research being communicated? Who are the target audiences for this research work? Are the research findings freely available and published in open access sources, if not why not? Will interested parties be able to see the primary

data, if so how and if not why? Is the presentation of the research outcomes suitable for audiences who may use it in professional or public policy decision-making? Does the research publication clearly state the methods and the limitations of the research as well as the results? Will you publish or make available negative results?

Level 6 - Empowerment Level

This level focuses on empowerment of others in the process of doing the research and in terms of how the research outcomes can empower others.

For example, has this research work empowered others in terms of building research capacity and supporting career development? How are the issues of equality, diversity and inclusion operationalised with the project work? Have you considered gender issues? How are research contracts operationalised, are they fair? How does the outcomes of the research work support empowerment of others, in terms of greater equality, diversity and inclusion?

Level 7 - Engagement Level

This level focuses on engagement practices within the project work and asks questions related to how others have or will be engaged with the research work from the planning through to the process of dissemination.

For example, do you have an engagement strategy for this research work? Are, and if so how, are stakeholders or publics involved in the research work? Is there wider participation in study design? Is there engagement with key communities and if yes when? How will you engage stakeholders and publics when sharing results? Are you engaging 'others' as you seek access to resources and have you consider how benefits from the research can be shared? Have you consider engaging with policy-makers at an early stage of the research planning?

Level 8 - Ethical Level

This level focuses on considering the overarching ethical level which encompasses all of the other levels and asks some prominent ethical questions related to the research work. All of the other levels are asking ethical questions, but this level asks researchers to ask some of the key overarching questions.

For example, are there overarching assumptions embedded in the project work that relate to societal norms? Is the research planning affected by the positionality of the

researchers? Does this research need to be conducted, could other approaches be used such as social innovation rather than technological innovation? Are there any alternatives to this approach? Could elements of the research plan be reduced, refined, or replaced?

This 8Es approach can be operationalised in the form of a table (see Annex 1) or further developed as a checklist that can act as a holistic approach, which can be used by researchers to map out and then consider how they will manage the issues raised by their planned research. It complements existing checklist approaches that are used by organisation such as the European Commission when asking researchers to set out the issues raised by their research. It is hoped this approach will be useful for researchers within the VetBioNet community in the longer term, as a planning tool and as a tool that can be used by research teams to support reflective planning.

5 Summary

This report has set out aspects of scoping and mapping of the issues highlighting the importance of mapping key ethical issues through the lens of Principles, Practice and Policies. Principles refers to guiding principles such as the discussion of the importance of the 3Rs approaches in animal infectious disease research. Practice refers to how aspects are operationalised and this has been highlighted through the example of the review processes of Animal Welfare Review Bodies and tools to support decision-making related to Humane Endpoints in animal experimentation. Policies refer to the role of regulation and the embedding of ethical principles such as the 3Rs consistently across institutions in Europe and how harmonisation can support good practice. Further work has been conducted on this policy aspect with the WP4 and specific deliverables have been produced.

Alongside this there is also a recognition that a number of tools and frameworks can support reflective analysis. For the development of new technologies and research programmes, frameworks such the Ethical Matrix approach and a 8Es approach can support researchers as they characterise, analyse and respond to the ethical aspects raised by their work. The Ethical Matrix can act as a useful mapping tool for this field of research and the 8Es framework can help researchers as they develop research ideas and plans. The development and provision of training that focuses on ethics by design and 3Rs also supports reflective practices. Training such as the FELASA

training (2019; 2022) and the ECR Summer School (2021) activities have supported reflective practices for those involved in delivering the training as well as receiving the training. These ethical approaches, training and frameworks should be helpful in supporting the long-term research activities and ambitions of this animal infectious disease research network.

If you have any comments on this report, please contact the authors as your comments would be gratefully received. Please contact Kate Millar (kate.millar@nottingham.ac.uk)

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7 Annexes

Annex 1: 8E Approach to Ethical Research Design and Management

Approach to encourage reflection on the (Ethical) **Validity of Research** plans and how these can be assessed at **8 levels** (i.e. an approach to ask a wide range of relevant questions of scientific research and the application of any knowledge produced from this research):

8E Approach: (1) *Empirical*, (2) *Experimental*, (3) *Epistemology*, (4) *Effects*, (5) *Evidence*, (6) *Empowerment*, (7) *Engagement* and (8) *Ethical levels*

Empirical Level (e.g. Data integrity, Ownership of data, etc)
Experimental Level (e.g. Experimental design, Ethical review of experiments, etc)
Epistemology Level (e.g. Pursuit of knowledge, What do we know, Disinterestedness, Research Method Assumptions, etc)
Effects Level (e.g. What might be the implications of your research on ethical relevant others)
Evidence Level (e.g. Science Communication, Open Science, Access to primary data, etc)
Empowerment Level (e.g. Research Capacity Building, Issues of Equality and Diversity, Fair Contracting, etc)
Engagement Level (e.g. Participation in study design, Engagement with communities, Sharing results, Access and benefit sharing, Collaboration with policy-makers, etc)
Ethical Level (e.g. What and who are ethical relevant, Checking alternatives, framing of the problem, Assumptions about all levels, etc).

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