Response from the Royal Society of Biology
to Defra's request for views and relevant information on potential implications of the use of Digital Sequence Information (DSI) on genetic resources for the three objectives of the Convention on Biological Diversity (CBD) and for the objective of the Nagoya Protocol on Access and Benefit Sharing (ABS).

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The Royal Society of Biology (RSB) is a single unified voice, representing a diverse membership of individuals, learned societies and other organisations. We are committed to ensuring that we provide Government and other policy makers, including funders of biological education and research, with a distinct point of access to authoritative, independent, and evidence-based opinion, representative of the widest range of bioscience disciplines.

1. Introduction and position

1.1 The Royal Society of Biology welcomes this opportunity to offer the following points in relation to the request for information on this important topic. Our membership have brought their views to our attention raising significant concerns in many quarters. These make clear that there is strong opposition to the inclusion of Digital Sequence Information (DSI) relating to genetic resources into the scope of the Nagoya Protocol. The RSB does not support the current proposals.

1.2 Our membership are in agreement that all countries should have a right to share in the benefits of research and there is an ethical requirement to have a clear framework for benefit sharing where research directly involves the collection and use of material/ samples from other countries, as in the generation of sequence data. We understand the premise behind inclusion of DSI under the Nagoya Protocol as a framework for benefit sharing, in that providing a framework could align legislation with growth in research scope, providing an international example and benchmark for individual countries to follow, and allowing for more consistent standards. However, we are concerned that the motion to add DSI on genetic resources under the scope of the Nagoya Protocol is not the appropriate way to implement this and would be counterproductive - threatening the use of this information for the global good - through critical impacts on the functioning of research and development activities.

2. Concerns relating to implementation of the legislation

2.1 Of initial concern is the level of precision, and efficiency and effectiveness of implementation expected to be provided by such regulation. This is of relevance, for example, to microorganisms, which are ubiquitous and readily cross national borders without human intervention. The origin of genetic sequence data, both in terms of the species of organism and its geographic origin, may frequently be unclear (e.g. those deriving from a river flowing through multiple countries). The wide spread and complex distribution of microorganisms and other biological entities also introduces a challenge for regulation through the potential for a lack of clarity on the precedence of the origin of genetic material. A hypothetical example could involve a researcher in Country 1 who may in the past have carried a microbe back on their clothing or equipment from an over-seas trip to Country 2. The researcher may culture that microbe inadvertently (through contamination of a sample collected in Country 1 perhaps) and deposit related DSI in a database. The microbe might then be identified in Country 2 some time later, with DSI generated from this sample too. In such a case, defining the true provider party may be difficult and would require considerable clarity and precision in legislation and regulation.

2.2 Furthermore, microorganisms are also difficult to consistently categorise at phenotypic and genotypic level. Therefore, the definition of a 'unique' genetic sequence for purposes of precision in legislation and regulation under the Nagoya Protocol is likely to be fraught with complexity (e.g. would a unique sequence be one that has no other 100% identical match in the current public databases or would 0.1% or a single nucleotide difference be enough to define it as unique?).

2.3 <u>Sector example:</u>
amoA genes (encoding a subunit of a functional gene) can be used to study soil ammonia oxidisers. All soils studied contain this gene but the sequence diversity is enormous. Sequences can be clustered, and there are some links between clusters and phenotypic characteristics, but there is little evidence that different phenotypes result from differences in amoA sequences. So, it is likely that discovery of a gene with an interesting function in one country can readily lead to the discovery of a gene with the same function, but with some differences in sequence, in another country. The development of bioinformatics- tools that can identify functional genes without phenotypic characterisation or even without their expression in host organism- adds further complexity to this issue.

3. Concerns relating to open access to data

3.1 Whilst a solution to the issues explained above may be to maintain the confidentiality of DSI resources, a lack of open access to these data is an extremely significant concern for the bioscience community. Our members cite the increasing demand for open data at national and global levels. This open access resource is not only of value to researchers, but also benefits third parties, such as farmers.

3.2 Sector examples:

Orphan crops, under-researched crops and landraces suffer from a lack of research and resources. Additional permits and bureaucracy could strain limited budgets or deter respective research. One of our members alerted us to the case of an under-researched crop, vital to several national economies, for which extensive DSI has already been generated but is not openly available to scientists, due to commercial and political concerns. This had noticeably hindered research progress. Additionally, from the sole perspective of the UK, plant science is considered among the country's strengths[1] and plant breeding in the UK has been estimated to return £40 for every £1 invested[2]; open access to genetic resources and especially DSI is vital to these activities.

3.3 Research advances by sharing information. The use of DSI in research allows for swift compilation, comparison and reanalysis of genetic information from a variety of sources, across multiple databases and gene sequences. The field of bioinformatics research, in addition to other research disciplines, relies heavily on this level of open access in DSI. Applying for ABS agreements to allow legal access to each sequence and/or database throughout the process of a single such research process represents a substantial administrative burden and delay to progress.

3.4 In all research areas, open access to data is fundamental to temporal and financial cost efficiency in collaboration and the use of shared and finite research resources; to research transparency; to the free flow of knowledge and sharing of the genetic information on novel species and new research breakthroughs; to publication in reputable journals; and in general to the continued development and growth of global research and development, both within and external to the life sciences sector.

3.5 Sector example:

Most microbiome studies are not 'self-contained' and rely on the ability to compare 16S rRNA gene sequences obtained from different studies and available in public databases. The same applies increasingly to studies of functional genes and of genomes and metagenomes.

4. Concerns relating to challenges for international biosecurity and health

4.1 Our community has also advised us of their concern relating to how the inclusion of DSI in the scope of the Nagoya Protocol may challenge national and international biosecurity and public, animal and plant health responses, by impeding international research and surveillance activities relating to existing and emerging global health threats. Such research may involve tackling disease outbreaks and the emergence of drug resistance through the development of effective, reliable prophylactic measures (e.g. vaccines), diagnostics and treatment (e.g. pharmaceuticals) for pathogens, pests and invasive species.

[1] UK Plant Sciences Federation (2014) UK Plant Science: Current status and future challenges, London, available at https://www.rsb.org.uk/images/pdf/UK_Plant_Science-Current_status_and_future_challenges.pdf, last checked 07/07/17.
[2] DTZ (2010) economic Impact of Plant breeding in the UK, Manchester, available at https://www.bspb.co.uk/sg_userfiles/BSPB_Plant_Breeding_Matters_Spring_2016.pdf, last checked 07/07/17.

4.2 Sector examples:

The continuous sharing and availability of pathogen samples and DSI in public databases is key to enable timely and accurate epidemic risk assessment and rapid response. Many of these efforts relate to diseases which disproportionately affect low and middle income countries, such as cholera and malaria. Timely sharing is essential for generating actionable public health information about how to prevent and respond to outbreaks. A patchwork of national regulations on the use and sharing of DSI would be a real barrier to these and other key global health efforts. The field of genomics has thrived on the basis of free and unrestricted sharing of genomic sequence data. Any restrictions on accessing genomic sequence data could create a major barrier to research and innovation that utilises this information, for example, the collation of sequence information to track the emergence of drug resistance on a global scale. There is a risk that the Nagoya Protocol could be implemented by countries in a way that hinders international scientific collaboration, threatening networks like MalariaGEN[3], an international community of researchers working to understand the genetic variation in humans, malaria parasites and mosquitoes to develop more effective ways to control malaria.

4.3 The ability to test for non-native threats will also be greatly hampered if scientists are restricted in the range of DNA sequences they can use when designing new diagnostics. This impacts not only on individual nations but also the global community, for example the development of international protocols under the Intergovernmental Panel on Climate Change (IPPC)[4] or the World Organisation for Animal Health (OIE)[5].

5. Concerns relating to legal, temporal and financial barriers to research

5.1 Additional community concerns relate to the legal and financial barriers encountered by researchers if DSI were to be included under the scope of the Nagoya Protocol. Such legislative and resultant regulatory requirements may lead to increased pressure on research institutions to pay legal fees to negotiate the terms of use of DSI on genetic resources (e.g. proving source and uniqueness). Academic and public institutions often generate freely accessible and beneficial outputs from research, on already tight budgets, and further legal and financial competition could hamper this. It was also suggested that the inclusion of DSI under Nagoya could make certain future research projects unaffordable or unappealing, with developers and investors potentially discouraged by the likely knock-on effects of adhering to increased complexity in the legislation (for example, when defining uniqueness and origin of the genetic resource and/or DSI). This may also impact the level of detail required for registration for Intellectual Property (IP) rights, since, under current patent law, a “non-obvious” or “novel” use must be described for the material to be granted patent, which may be difficult to ascertain, in relation to the previously described difficulty in proving uniqueness within DSI from certain organisms. This trend of increasing complexity in research activities may lead to research focusing away from using genetic material or DSI from provider parties. Furthermore, since many research projects are run by teams of collaborators

[3] https://www.malariagen.net/
[4] http://www.ipcc.ch/
[5] http://www.oie.int/

affiliated to a variety of institutions on a national and/or international scale, it is unclear how the outputs/ benefits from such research, due to the provider party, would be divvied across these collaborators, particularly if certain institutions are based in low and middle income countries and are thus already under financial pressure.

5.2 Unlike many biological samples, DSI can be reused indefinitely. If DSI were to be incorporated under the scope of Nagoya, this could result in an ever increasingly complex picture involving multiple agreements on benefit sharing for any given genetic sequence, which would be attached to the sequence forever, with each further transfer requiring additional permission and documentation resulting in long term and increasing litigation burden, financial and time delays to research and innovation.

5.3 Sector example:
Members have pointed out that the proposal to include DSI under the scope of Nagoya is in some ways analogous to the early case of the privately-funded Human Genome Project (HGP)[6] which held access restrictions and intellectual property restrictions, including reach-through rights, on the data generated. Provision of public sequence, freely available to all, was seen as a major step forwards in this case.

6. Concerns relating to the independence of scientific research

6.1 Finally, the moral dilemma relating to the use of scientific knowledge being regulated by national governments was raised as a potential threat to the independence and growth of scientific research and innovation.

7. Conclusions and potential alternatives to Nagoya

7.1 Overall, the underlying concern for our members is that the inclusion of Digital Sequence Information (DSI) relating to genetic resources into the scope of the Nagoya Protocol will introduce extra bureaucratic stages to research and development, thus delaying scientific progress in many important areas. Members of the biosciences sector agree that whilst the principles that underpin the Nagoya Protocol are essentially sound, the bureaucratic mechanism by which the legislation could be developed to incorporate and implement regulation on DSI risks creating unnecessary barriers to research and development. Thus we believe that the disadvantages to this proposition outweigh any foreseeable benefits.

7.2 Careful consideration of the complex issues including and external to those highlighted above will be needed to define an alternative solution to cover the ethical considerations relating to the use of DSI in research. An agreed proposal is needed and therefore further and wide stakeholder engagement required, both within and external to the bioscience sector, and from

[6] https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/

relevant private organisations, public bodies and government departments in the UK and internationally. Examples of such organisations include learned societies (the RSB would welcome any further opportunity to provide advice and comment), the UK Synthetic Biology Leadership Council[7], the UK BioIndustry Association[8], the European Federation of Biotechnology[9], and other bodies that represent research organisations and industry. We welcome the effective and efficient work of colleagues in Regulatory Delivery who are active in their endeavour to improve community awareness of the implications of the Nagoya Protocol, however, our observation is that awareness of the implications of inclusion of DSI in the Protocol is generally low, and this should be developed in a similar manner, through accessible and proactive guidance. Such guidance may involve case studies that demonstrate the value of international genomics collaborations, such as H3Africa[10] and MalariaGEN[3] and the value of publicly available and accessible databases of genetic information, such as the Genome Online and Online Mendelian Inheritance in Man databases.

7.3 Alternative systems to Nagoya that are currently in use should be sought out, considered and assessed. For example, in China and Brazil patent applications require information on the origin of the genetic resources used. Equally, policies are currently in use by publishers, data repositories and funders regarding open access to data; these should be upheld if DSI is accessed in isolation from the original genetic material. Any mechanism used to ensure benefit sharing should be proportionate and seek to avoid limiting the ability of researchers and other global health professionals to collaborate and share the materials and outputs of their research, such as DSI.

7.4 We suggest that a framework for allowing access and benefit sharing relating to research utilising DSI should take into account the **research outcome** expected, i.e. the ultimate use of the sequence information. Our members suggested that, within this, clearer definition is required of the use of bioresources for purely commercial application and profit versus application for broader societal benefit (e.g. public health benefit/ biosecurity).

7.5 It has been suggested that the World Health Organisation[11] may be an appropriate source of knowledge on proportionate frameworks to ensure the benefit sharing of research based on DSI, which do not hinder epidemic preparedness and response efforts, international research collaborations and resources.

[7] https://www.gov.uk/government/groups/synthetic-biology-leadership-council
[8] https://www.bioindustry.org/home/
[9] http://www.efb-central.org/
[10] https://h3africa.org/
[11] http://www.who.int/en/

The Society welcomes the Department's consultation on DSI in relation to the Nagoya Protocol. We are pleased to offer these comments which have been informed by specific input from our members and Member Organisations across the biological disciplines. The RSB is pleased for this response to be publicly available. For any queries, please contact the Science Policy Team at Royal Society of Biology, Charles Darwin House,12 Roger Street, London, WC1N 2JU. Email: policy@rsb.org.uk

Appendix A

Member Organisations of the Royal Society of Biology

Full Organisational Members
Academy for Healthcare Science
Agriculture and Horticulture Development Board
Amateur Entomologists' Society
Anatomical Society
Association for the Study of Animal Behaviour
Association of Applied Biologists
Bat Conservation Trust
Biochemical Society
British Andrology Society
British Association for Lung Research
British Association for Psychopharmacology
British Biophysical Society
British Crop Production Council
British Ecological Society
British Lichen Society
British Microcirculation Society
British Mycological Society
British Neuroscience Association
British Pharmacological Society
British Phycological Society
British Society for Cell Biology
British Society for Developmental Biology
British Society for Gene and Cell Therapy
British Society for Immunology
British Society for Matrix Biology
British Society for Medical Mycology
British Society for Nanomedicine
British Society for Neuroendocrinology
British Society for Parasitology
British Society for Plant Pathology
British Society for Proteome Research
British Society for Research on Ageing
British Society of Animal Science
British Society of Plant Breeders
British Society of Soil Science
British Toxicology Society
Daphne Jackson Trust
Drug Metabolism Discussion Group
Fondazione Guido Bernardini
GARNet
Genetics Society
Heads of University Centres of Biomedical Science
Institute of Animal Technology
Laboratory Animal Science Association
Linnean Society of London
Marine Biological Association
Microbiology Society
MONOGRAM – Cereal and Grasses Research Community
Network of Researchers on Horizontal Gene Transfer & Last Universal Cellular Ancestor
Nutrition Society
Quekett Microscopical Club
Royal Microscopical Society
SCI Horticulture Group
Science and Plants for Schools
Society for Applied Microbiology
Society for Experimental Biology
Society for Reproduction and Fertility
Society for the Study of Human Biology
Systematics Association
The Field Studies Council
The Physiological Society
The Rosaceae Network
Tropical Agriculture Association
UK Environmental Mutagen Society
UK-BRC – Brassica Research Community
UK-SOL – Solanacea Research Community
University Bioscience Managers' Association
VEGIN – Vegetable Genetic Improvement Network
Zoological Society of London

Supporting Organisational Members
Affinity Water
Association of Medical Research Charities
Association of the British Pharmaceutical Industry (ABPI)
AstraZeneca
BASIS Registration Ltd.
Bayer
BioIndustry Association
Biotechnology and Biological Sciences Research Council (BBSRC)
British Science Association
Envigo
Fera
Forest Products Research Institute
Institute of Physics
Ipsen

Medical Research Council (MRC)
MedImmune
Pfizer UK
Plant Bioscience Limited (PBL)
Porton Biopharma
Procter & Gamble
Royal Botanic Gardens, Kew
Royal Society for Public Health
SynBiCITE
Syngenta
The Ethical Medicines Industry Group
Understanding Animal Research
Unilever UK Ltd
Wellcome Trust
Wessex Water
Wiley Blackwell