Professor [redacted]
University of Birmingham

Date: 23rd April 2021
Our ref: FS900092

Dear Mark,

Supply of 2020 Fellowship in Computational Toxicology - Advancing in silico methods of assessing toxicological risk

Following your tender/ proposal for the supply of **FS 900092 - 2020 Fellowship in Computational Toxicology - Advancing in silico methods of assessing toxicological risk** to FSA, we are pleased confirm our intention to award this contract to you.

The attached contract details ("**Order Form**"), contract conditions and the ***Annexes*** set out the terms of the contract for the provision of the deliverables set out in the Order Form.

We thank you for your co-operation to date and look forward to forging a successful working relationship resulting in a smooth and successful delivery of the deliverables. Please confirm your acceptance of the Conditions by signing and returning the Order Form within **7** days from the date of this Order Form. No other form of acknowledgement will be accepted. Please remember to include the reference number above in any future communications relating to this contract.

We will then arrange for Order Form to be countersigned which will create a binding contract between us.

Yours sincerely,

[redacted]

Order Form

1. Contract Reference	FS900092	
2. Date	23rd April 2021	
3. Buyer	Food Standards Agency Foss House Peasholme Green York YO1 1PR	
4. Supplier	[redacted]	
5. The Contract	The Supplier shall supply the deliverables described below on the terms set out in this Order Form and the attached contract conditions ("**Conditions**") and any **Annexes.** Unless the context otherwise requires, capitalised expressions used in this Order Form have the same meanings as in Conditions. In the event of any conflict between this Order Form and the Conditions, this Order Form shall prevail. Please do not attach any Supplier terms and conditions to this Order Form as they will not be accepted by the Buyer and may delay conclusion of the Contract.	
6. Deliverables	**Goods**	Not Applicable
	Services	As detailed at: **Annex 2 – Specification** and **Annex 3 – Suppliers Proposal**
7. Specification	The specification of the Deliverables is as set out in **Annex 3 – Supplier's Proposal.**	

8. Term	The Term shall commence on **2nd August 2021** and the Expiry Date shall be **1st August 2025** unless it is otherwise extended or terminated in accordance with the terms and conditions of the Contract. The Buyer may extend the Contract for a period of up to 6 months by giving not less than 10 Working Days' notice in writing to the Supplier prior to the Expiry Date. The terms and conditions of the Contract shall apply throughout any such extended period.
9. Charges	The Charges for the Deliverables shall be as set out in **Annex 4 – Suppliers Financial Proposal.**
10. Payment	All invoices must be sent, quoting a valid purchase order number (PO Number), to: [redacted] Within **10** Working Days of receipt of your countersigned copy of this letter, we will send you a unique PO Number. You must be in receipt of a valid PO Number before submitting an invoice. To avoid delay in payment it is important that the invoice is compliant and that it includes a valid PO Number, PO Number item number (if applicable) and the details (name and telephone number) of your Buyer contact (i.e. Contract Manager). Non-compliant invoices will be sent back to you, which may lead to a delay in payment.
11. Buyer Authorised Representative(s)	For general liaison your contact will continue to be: [redacted]
12. Address for notices	**Buyer:** [redacted] **Supplier:** Legal Notices: Director of Research Support Services, Finance Office, [redacted]
13. Key Personnel	As detailed in **Annex 3 – Supplier's Proposal**

14. Procedures and Policies	The Buyer may require the Supplier to ensure that any person employed in the delivery of the Deliverables has undertaken a Disclosure and Barring Service check. The Supplier shall ensure that no person who discloses that he/she has a conviction that is relevant to the nature of the Contract, relevant to the work of the Buyer, or is of a type otherwise advised by the Buyer (each such conviction a "**Relevant Conviction**"), or is found by the Supplier to have a Relevant Conviction (whether as a result of a police check, a Disclosure and Barring Service check or otherwise) is employed or engaged in the provision of any part of the Deliverables.

Signed for and on behalf of the **Supplier**	Signed for and on behalf of the **Buyer**
[redacted]	[redacted]

Annex 1 – Authorised Processing Template

Contract:	**FS900092**
Date:	
Description Of Authorised Processing	**Details**
Subject matter of the processing	The Parties agree that no Personal Data shall be processed or managed by the Supplier as part of this Contract, unless subsequently confirmed by the exchange of a Variation to Contract.
Duration of the processing	
Nature and purposes of the processing	
Type of Personal Data	
Categories of Data Subject	

Annex 2 - Specification

GENERAL INTRODUCTION

The Food Standards Agency is an independent Government department working across England, Wales and Northern Ireland to protect public health and consumers wider interest in food. We make sure food is safe and what it says it is.
The Agency is committed to openness, transparency and equality of treatment to all suppliers. As well as these principles, for science projects the final project report will be published on the Food Standards Agency website [redacted] For science projects we will encourage contractors to publish their work in peer reviewed scientific publications wherever possible. Also, in line with the Government's Transparency Agenda which aims to encourage more open access to data held by government, the Agency is developing a policy on the release of underpinning data from all of its science- and evidence-gathering projects. Data should be made freely available in an accessible format, as fully and as promptly as possible. Consideration should be given to data management as new contracts are being negotiated. Resource implications for this should be taken into account. The mechanism for publishing underpinning data should allow the widest opportunity for to enable its re-use. Where possible, underpinning data should be included in the final project report. Where data are included in the final report in pdf format, they should also be published separately in a format that can be used for further analysis. Large data sets can be provided separately in an annex to the report, and published, where possible, alongside the final report online Where it is more appropriate to publish underpinning data in an existing database, archive, repository or other community resource, or for data to be saved in a specialist proprietary format, information will be provided on how the data can be accessed. There will be some circumstances where release of data may need to be restricted or anonymised for reasons of commercial and/or personal sensitivities.

The main objective from the FSA's Strategic Plan for 2015-2020 to which this work would align is to protect consumers from unacceptable risks which may arise in connection with the consumption of food (including risks caused by the way in which it is produced or supplied) and otherwise to protect the interest of consumers in relation to food. This includes protecting consumers from chemical risks, where possible to ensure food is safe.

This work is being commissioned under the FSA strategic evidence fund and the funding of fellowships in celebration of the 20th anniversary of the FSA. This fellowship will support the work of the chemical risk assessment team in providing accurate risk assessments.

A. THE SPECIFICATION

Background

In silico (computational) methods of assessing toxicological risk are being developed by industry and other regulators as a cheaper, rapid alternative method to animal and human testing models. The FSA and COT recently held a workshop on dose response modelling which highlighted the diversity of *in silico* applications available,

including artificial intelligence, modelling of physiologically-based pharmacokinetics (PBPK), benchmark dose modelling and adverse outcome pathways (AOPs).

The FSA needs to understand the opportunities and limitations of the tools available and uncertainty associated with them to ensure we can utilise appropriate tools and provide governance in this area. A number of potential research ideas came from the workshop including computational molecular docking for potency estimation, toxicodynamic modelling and AOPs in relation to molecular docking, PBPK modelling to predict biomarkers for which the UK has a lot less data than the EU.

Objectives:

- Create a hub at FSA for the interested community;

- Engage and map the research community and industry in the UK and overseas that can deliver and use any validated and/or cutting edge *in-silico* tools

- Evaluate the opportunity of using *in silico* models within FSA risk assessments where appropriate

Evaluate the opportunity of including *in silico* outputs as part of FSA risk assessments where appropriate

- Investigate the uncertainties associated with such models.

- Scope and review emerging technologies

- Bring in/design relevant models/technologies to be used by the FSA in risk assessment and include appropriate training of FSA staff,

- Ensure validation of model and QA/QC meets with FSA policies/requirements

- Ensure that FSA staff are fully trained in the use of any model/technology brought in-house or developed

- Cross fertilisation of ideas with experts in other chemical areas e.g. cosmetics and industrial chemicals and learning from each other as we develop 21st century methods and strengthening our 3Rs commitment.

The Specification

Tenders are invited to:

- Carry out recruitment and employment of an appropriate fellow with a background in computational toxicology and/or the use of *in silico* modelling, with respect to chemicals. The fellow will also need an understanding of toxicology.
- Provide practical resources and support to this fellow to help them identify key areas of interest for the FSA and produce suitable outputs
- Support the fellow in working full time on this fellowship with 85% of their time to be spent within the FSA (offices or virtually) with the remaining 15% of their time spent at the University collaborating and networking with experts in the field. The time at the FSA is to learn and understand FSA procedures and

processes and identify useful outputs which would benefit the risk assessment process. There will also be regular meetings between the FSA, the fellow and the supervisor to discuss ideas (scoping phase) and agree milestones and break points to ensure adequate progress is being made. Regular meetings will take place for the duration of the fellowship.

- Support the fellow as ultimately, the FSA would like the fellow to establish a novel tool or develop an existing tool that would be of value beyond the life of the fellowship and aid in FSA risk assessment long term. A novel tool should be compatible with FSA systems and "future proof" against developments in IT systems and the FSA should have full access and ownership where possible.
- Help the fellow establish a hub engaging FSA, SAC members and others with *in silico* data and industry/academia.

Main outputs:

- Published reports and bespoke technical reports focussed on recommendations for enhancing risk assessment through the use of *in silco* technologies;

- Established hub engaging FSA, SAC members and others with *in silico* expertise in industry and academia.

- Dissemination of information through workshops within and wider than the FSA

The specification must:

Include points which address the following:

Innovation

Development of a (proprietary) tool to aid the use of computational methods in risk assessment of chemical hazards for the FSA.

Risk

Things to consider:

Contractor related: Fellow leaves organisation; Supervisor leaves organisation; organisation ceases to exist or no longer receives funding; EU exit; failure to recruit an appropriate fellow; Covid-19 (or similar) related restriction of access to systems/necessary data/papers;

FSA related: Restrictions imposed by FSA IT systems

Ethics

Undertaken work will not include any human or animal subjects. Any data should be covered by data protection (see below).

Data protection

Any proprietary data used in development of the system will remain confidential and will be shared with the contractor in confidence and only with permission of the data owners.

Data security

Please confirm in your tender that you have in place, or that you will have in place by contract award, the human and technical resources to perform the contract to ensure compliance with the General Data Protection Regulation and to ensure the protection of the rights of data subjects.

Please provide details of the technical facilities and measures (including systems and processes) you have in place, or will have in place by contract award, to ensure compliance with the General Data Protection Regulation and to ensure the protection of the rights of data subjects. Your response should include, but should not be limited to facilities and measures:

- to ensure ongoing confidentiality, integrity, availability and resilience of processing systems and services;
- to comply with the rights of data subjects in respect of receiving privacy information, and access, rectification, deletion and portability of personal data;
- to ensure that any consent-based processing meets standards of active, informed consent, and that such consents are recorded and auditable;
- to ensure legal safeguards are in place to legitimise transfers of personal data outside the EU (if such transfers will take place);
- to maintain records of personal data processing activities; and

to regularly test, assess and evaluate the effectiveness of the above measures.

Dissemination and exploitation

Anticipated outputs include:

Publishable reports and bespoke technical reports focussed on enhancing risk assessment through the use of *in silico* technologies.

Better engagement between industry, academia and the FSA and other regulators in this area.

Most importantly, improved ability to deal with incidents involving chemicals with limited/no available toxicological/potency data on which to base the risk assessment.

Ultimately, the established tool needs to be of value beyond the life of the fellowship and aid in risk assessment long term. Before completion of the fellowship, members of the FSA will need to have been fully trained in the use of the developed tool.

Openness:

FSA has values and specific policy on being open and transparent, which includes publishing the full dataset of its research and surveillance studies. Both the lead contractor and their sub-contractors must agree to this openness policy. Any potential issues with this should be highlighted within the proposals.

Sustainability

Ultimately, the established tool needs to be of value beyond the life of the fellowship and aid in risk assessment long term. Before completion of the fellowship, members of the FSA will need to have been fully trained in the use of the developed tool.

Quality

Model validation and QA/QC need to be undertaken (at a minimum of the requirements of the FSA (MSRO checklist)) as part of the project.

The quality assurance considerations need to include how the work will meet the standards in the Aqua Book:

[redacted]

The agreed applicable sections of the Joint Code of Practice for research should be adhered to: [redacted]

Annex 3 – Supplier's Proposal

Key information

Full name and title of lead applicant	[redacted]
Organisation	University of Birmingham
Department	School of Biosciences
Address and postcode	[redacted]
Telephone No	[redacted]
Email address	[redacted]

Project title and reference number: Advancing in silico methods of assessing toxicological risk (Ref. FS900092)

Proposed start date: 2nd August 2021

Proposed end date: 1st August 2025

1. Summary and Objectives

A: Please give brief details of your proposed work in no more than 400 words:

Our approach to the proposed work, and indeed to our other translational toxicology projects, is distinctly unique. Rather than push cutting-edge academic-led science towards regulators and end users, we integrate those in need of scientific solutions into project planning, implementation and dissemination. Our approach has already been tried and implemented by our on-going engagements with other regulatory agencies who have articulated similar commitments to those 21st century methods expressed in this FSA call: at exploring, understanding and implementing computational NAMs in risk assessment. Over the last 4 years we have introduced NAMs to the European Chemicals Agency (ECHA), through a competitive framework contract, delivering translational projects, training courses, and supporting this agency at meetings.

The proposed work will consist of (a) listening, scoping, reviewing and understanding FSA's problem space, (b) resulting in customised training and network-building around the co-production

of specific case studies, (c) that lead towards an increasing regulatory acceptance of computational NAMs, and (d) in-house expertise and practical solutions to FSA's risk assessment challenges. In short, we have evidence-based knowledge that success can only be achieved by a true integration of expertise from the FSA, University of Birmingham (UoB) and HSE Science and Research Centre, starting at the planning stages of this proposed multi-year project. Our four objectives, introduced below, include undertaking computational toxicology case studies. We propose the first of these is to develop and evaluate confidence in a new hazard assessment workflow that would integrate *in vitro* omics toxicity data, benchmark dose modelling and PBPK modelling, to serve as the basis for quantitative risk assessment for human health, i.e. towards generating human health-based safety thresholds for the FSA and other regulators.

Our team is internationally recognised, most recently recognised by a UoB-led 20M Euro H2020 project *PrecisionTox* – that seeks to establish a new, 3Rs-compliant, cost-effective testing paradigm for chemical safety assessment that revolutionises regulatory toxicology, replaces animal testing, reduces uncertainty, and determines safety factors in assessing risks to human health. In addition, the computational infrastructure at UoB is well-placed to support this FSA project, including one of the largest academic IBM Power AI clusters in the UK. Of added value to this proposed partnership: (a) our MSc programmes in both Bioinformatics (available online, from 2021) and Toxicology, and (b) expertise in legal frameworks for chemical safety - because of our realisation some years ago that changes in chemical risk assessment cannot be driven by science alone.

B: Objectives and relevance of the proposed work to the FSA. Please detail how your proposed work can assist the agency in meeting its stated objectives and policy needs. Please number the objectives and add a short description. Please add more lines as necessary. The anticipated activities and outputs are described in the invitation document:

Overall aim: To develop a strategic partnership between the Food Standards Agency (FSA), University of Birmingham (UoB) and Health and Safety Executive's Science and Research Centre to capitalise upon recent and on-going developments in New Approach Methodologies (NAMs) - including computational methods and modelling approaches - to more reliably risk assess food-related chemicals.

Specific objectives:

1. To **deeply scope** the FSA's problem space in chemical risk assessment and to (a) map this to our computational NAMs solution space, thereby (b) aiding the FSA to **develop a strategy for the utilisation of NAMs**, to (c) ultimately provide leadership (i.e., a community hub) by proposing and undertaking inclusive case studies.
2. To ensure that the FSA is trained for the internal use of computational NAMs by delivering in-depth **training courses** for FSA scientists, including an introduction to existing and emerging NAM technologies, and topics selected from the FSA's NAM strategy (Objective 1), e.g., benchmark dose modelling to derive molecular points of departure,

physiologically-based pharmacokinetics (PBPK) modelling for *in vitro* to *in vivo* extrapolation, multiview machine learning applied to biomarker discovery.

3. To develop and evaluate confidence (i.e., quality assurance and quality control (QA/QC)) in a new **hazard assessment workflow** that integrates *in vitro* omics toxicity data, benchmark dose modelling and PBPK modelling to serve as the basis for quantitative risk assessment for human health, i.e. towards generating human health-based safety thresholds for FSA and other regulators (Case Study 1).
4. To develop and deliver a second **case study** that fortifies the community-wide acceptance of 21st century methods in risk assessments, to accelerate the successful application of NAMs within the FSA.

The mapping of these objectives to the FSA specification is described in detail in Section 2B.

2. Description of approach/scope of work

A: Please can you describe your approach to identifying and recruiting the fellow. The FSA would wish to be represented on an interview panel or meet anyone currently employed who is being considered for the role prior to signing of the contract. The person would need to successfully complete FSA security checks. The fellow will have no FSA employment rights:

The Fellow will be identified via our extensive network of close collaborators across all relevant sectors invested in computational NAMs, who already see UoB as an ideal staging ground for their career development in 21st century regulatory science, yet who are likely to achieve real-world impact by this strategic alliance with the FSA. Therefore, FSA and UoB will jointly advertise this opportunity to attract and identify the best candidate based on selection criteria that will maximise the objectives of this fellowship. At UoB we utilise various advertising strategies, including traditional (i.e., websites, jobs.ac.uk, LinkedIn) and modern media (i.e., social media), as well as our extensive international network of scientists in NAMs and computational toxicology across academia, industry and governments. Our international networks include academic partners (e.g., through the H2020 *PrecisionTox* project led by UoB), Societies (e.g., our founding role in the Global SETAC Omics group), and regulatory organisations (e.g., through our participation in Accelerating the Pace of Chemical Risk Assessment consortium). The lead applicant (Viant) has successfully recruited 45 postdoctoral fellows into his team between 2005 and 2020, based on these proven approaches. We confirm that the FSA will participate in the short-listing of applications and the interview processes. Addressing any potential risks associated with the recruitment process is described in Section 6, Risk Management.

B: Please describe how you will meet our specification and summarise how you will deliver your solution. You must explain the approach for the proposed work. Describe and justify the approach, methodology and study design, where applicable, that will be

used to address the specific requirements and realise the objectives outlined above. Where relevant (e.g. for an analytical survey), please also provide details of the sampling plan. Please include anticipated IT requirements for the role, funding for which will come from the awarded funding:

Establishing a robust scientific basis for determining the risk to human health from exposure to chemicals would provide the foundation for global harmonisation of chemical safety assessments. This has been an ongoing initiative of the World Health Organization (WHO) that launched the International Programme on Chemical Safety (IPCS) in 1980 [1], and of the Organisation for Economic Co-operation and Development (OECD) through standardised test guidelines and the 'Mutual Acceptance of Data' [2]. There are two consistent and recurring themes that remain to be properly addressed in chemical safety assessment. The first is the need for human exposure and toxicity data, which are scarce. The lack of human toxicity data prolongs the reliance on animal studies. The second is the need to develop a common, transparent and reliable approach for biologically-based, quantitative, chemical safety assessments for chemicals of high economic value and high concern for authorisation [3]. These are now described as *New Approach Methodologies* (NAMs) for risk assessment, and are being strongly driven by the US Environmental Protection Agency, Health Canada and the European Chemicals Agency (ECHA), for example through the Accelerating the Pace of Chemical Risk Assessment consortium (ACPRA) [4]. The promise of NAMs is enabling a more precise derivation of health-based guidance values for regulators based on mechanistic knowledge.

Our team is deeply involved in multiple NAMs projects that are seeking to address both of these issues, in part as consultants to ECHA in NAMs, including the provision of expertise and services in omics technologies and computational toxicology. In addition, the University of Birmingham (UoB) leads a new 20M Euro H2020 project *PrecisionTox* – that seeks to establish a new, 3Rs-compliant, cost-effective testing paradigm for chemical safety assessment that revolutionises regulatory toxicology, replaces animal testing, reduces uncertainty, and determines safety factors in assessing risks to human health – uniting a highly interdisciplinary mix of genomics, metabolomics, evolutionary theory, computational toxicology, data science and law, to one common mission. Our team for the proposed FSA Fellowship also includes internationally-recognised expertise in PBPK modelling from the HSE Science and Research Centre (Dr George Loizou). While the ultimate solution for biologically-based, quantitative, chemical safety assessments necessarily spans wet and dry science, as utilised in the *PrecisionTox* project for example, in this proposal we focus on developing and implementing the computational solutions, utilising existing (and later in the 4-yr programme, new) datasets that have been derived from high-throughput, high information content omics technologies and targeted molecular assays.

Omics technologies, including transcriptomics (the measurement of gene expression following chemical exposure) and metabolomics (the measurement of functional biochemical changes following exposure), have been highlighted as promising and versatile tools for chemical risk assessment by regulatory bodies [5-7]. The strengths of these technologies for the measurement of molecular biomarkers include: the rapid detection of a broad range of molecular pathways of toxicity; measurements that have comparable sensitivities to traditional apical endpoints; and the technologies can be applied to *in vitro* test systems [8]. **Computational and data science**

approaches represent an absolutely essential component of NAMs, and for the analysis of omics and targeted molecular toxicity data. While the incorporation of molecular mechanistic information into regulatory toxicology will enable new risk assessment methods with greater certainty, such as using *molecular biomarkers as hazard flags*, these molecular markers first need to be discovered using **machine learning** and/or supervised multivariate statistical methods (e.g. Stemina Biomarker Discovery's devTOX *in vitro* assay that predicts developmental toxicity using metabolic biomarkers discovered using metabolomics [9]). Also, while NAMs can in principle *set safety thresholds*, these first need to be derived as molecular points of departure from omics concentration-response data using **benchmark dose analysis approaches** and compared to exposure levels [10-11]. While NAMs have been used to effectively *group chemicals into categories* with greater confidence [8,12], this relies on approaches to **calculate and visualise the similarities of omics responses**, e.g. BASF's use of metabolomics to group source and target substances, supporting the regulatory approval of 3-aminopropanol [13]. Most importantly, these technologies can derive mechanistic information from *in vitro* testing which is extrapolated to humans through **PBPK modelling** approaches [14].

Our approach to integrate the most relevant computational approaches into the FSA's chemical risk assessment procedures is based on hard evidence and lessons learned from the last 4 years of introducing NAMs to the European Chemicals Agency. We have achieved this through multiple parallel routes, centred around winning a competitive multi-year framework contract with ECHA for "Services related to metabolomics measurements and multi-omics data interpretation". Within this framework, we have conducted several translational research projects with ECHA, delivered three face-to-face training courses in NAMs (the most recent to the ECHA Member States Committee), and supported ECHA at four APCRA meetings since 2017. These experiences have taught us a lot about the challenges of delivering complex science into regulatory frameworks, including the necessity for the whole team to listen carefully and deeply understand the problem space, the importance of communicating the solution space effectively, and not least the considerable commitment of time and effort required for success. Consequently, we are well positioned to support the development of NAMs at the FSA, and our overall approach of integrating a deep scoping and strategy development exercise (**Objective 1**), the delivery of several training courses (**Objective 2**), as well as inclusive case studies (**Objectives 3 and 4**) reflects this experience (see Figure 1).

These objectives will be met by the full-time engagement of a computational toxicology Fellow with the FSA, supported by a team of academic experts from UoB who already collaborate effectively on a major international research initiative in the pursuit of *Precision Toxicology*. Specifically, to achieve success, we propose advancing many of the proposed objectives in parallel (Figure 1) allowing for iterative feedback on the programme in real time in terms of the relevance, equity for partnerships, interdisciplinarity, effectiveness and efficiency of the project. We propose an approach at the start of the project where the Fellow devotes ca. 50% of their time to scoping and strategy development (**Objective 1**), and their remaining time to begin a specific computational toxicology project (**Objective 3**). We have pre-selected this project - Case Study 1 - for an immediate start since the FSA have already highlighted their interest in benchmark dose modelling and PBPK modelling. At the mid-point of the 4-yr programme, i.e. on completion of the NAM strategy development (including several proposed case studies), we propose the Fellow can then begin a second, FSA-prioritised, Case Study 2 (**Objective 4**). Further details about our approach and methodologies are described in Section 3: Project Plan.

FSA requirements (where the text in italics has been copied from the FSA document inviting expressions of interest):

- Yes, we have identified research groups *with suitable experience and contacts*, and we will *carry out recruitment and employment of an appropriate fellow(s) with a background in computational toxicology or similar relevant field*. Yes, the FSA will *be represented on the interview panel*, and we welcome feedback from the FSA both at the applicant short-listing stage and at the interviews of potential candidates.
- Yes, both UoB and the HSE's Science and Research Centre will *provide practical resources and support to this fellow to help them identify key areas of interest for the FSA and produce suitable and tangible outputs.* Indeed, this is exactly the strategy that we propose based on our lessons learnt from engaging with ECHA (see Figure 1), combining scoping, strategy development, training and case study implementation phases, as described further in the project plan below.
- Yes, we will support the Fellow *working full time on this fellowship*, with their time distributed as 85% at the FSA (offices or virtually) with the remaining time at UoB/HSE. We have demonstrated since March 2020 that we can work online in a highly effective manner, although we welcome the return of some face-to-face interactions. The Fellow will have

access to *the University's resources, and will collaborate and network with experts in the field*. We will organise *regular meetings between the FSA, the Fellow and the supervisory team to discuss ideas and agree to milestones and break points to ensure adequate progress is being made* throughout the fellowship.

- Yes, *the Fellow [will] establish a novel tool or develop an existing tool or tools to aid the use of computational toxicology in risk assessment of chemicals and would be of value beyond the life of the fellowship and aid in FSA risk assessment long term* - as demonstrated by Case Study 1 that will focus on developing a hazard assessment workflow that integrates *in vitro* omics toxicity data, benchmark dose modelling and PBPK modelling.
- Yes, the new *tool should be compatible with FSA systems and "future proof" against developments in IT systems* - and this will be explored during the scoping phase. Yes the FSA would *have full access* to the tools - and we believe the tools need to be made fully open-access for the reasons presented in the introduction of our bid, that we seek global harmonisation of chemical safety assessments to achieve the benefits of reduced costs, increased numbers of chemicals tested more rapidly, and reduced animal testing.
- Yes, through our extensive international leadership roles in NAMs in toxicology, we will *help the fellow establish a hub engaging FSA, FSA Scientific Advisory Committee (SAC) members and industry / academia / public bodies.* This will be achieved in part through our existing roles and networking in APCRA, the OECD, and our new H2020 *PrecisionTox* project. In addition we are currently funded by various industry sectors to develop NAMs for risk assessment, including Consumer Products (Unilever) and Agrichemicals (Syngenta). While commercial confidentiality will of course have to be respected, our supervisory team can therefore bring perspectives from industry. Furthermore, we have commissioned market research to understand the views of industry to the use of NAMs in chemical risk assessment. Regarding public bodies, in addition to the framework contract in NAMs with ECHA, both the HSE Science and Research Centre and UoB engage with EFSA. At an international level, we have an active collaboration with the US Food and Drug Administration, evaluating the reproducibility of an omics technology for deriving a consistent grouping of chemicals (for read-across). This project is led by UoB and involves 8 ring-trial partners (industry, academia and government).

<u>Other objectives of the FSA fellowship that are not covered above:</u>

- *Ensure validation and QA/QC of any models designed for or brought into the FSA meets with FSA policies/requirements:* first we need to deeply understand FSA policies and requirements through the scoping phase, then ensure that these are met. We have experience in developing QA/QC standards as well as reporting standards for the use of molecular mechanistic data in chemical risk assessment, demonstrated through our leadership of the Ecetoc MERIT project (see below) and OECD Metabolomics Reporting Framework.
- *Ensure that FSA staff are fully trained in the use of any model/technology either brought in-house or developed*: this is addressed by our NAM training courses for FSA scientists.
- *Cross fertilisation of ideas with experts in other chemical areas, e.g. cosmetics and industrial chemicals, environmental risk assessment, chemical risk assessment and learning from each other as we develop 21st century methods and strengthening our 3Rs commitment:*

this has been addressed above, for example through our OECD and APCRA activities, and further demonstrated by our earlier and current awards from Ecetoc and Cefic.

Computational infrastructure:

Led by Professor [redacted](co-applicant), the **Centre for Computational Biology (CCB)** is a cross-campus initiative providing a broad expertise in Data Science for the Life Sciences from Bioinformatics, to Health Data Science and Precision Toxicology. With its 60 members from backgrounds as diverse as Mathematics, Statistics, Computer Science, Biology or Chemistry, the CCB aims to promote excellence in Computational Biology, Data Sciences, and Bioinformatics through both research and training. This has led to the establishment of the ***Compute and Storage for Life Sciences* (CaStLeS) initiative**, the key component of *Birmingham Environment for Academic Research local cloud* (BEARCloud) dedicated to Life Sciences, includes one of the **largest academic IBM Power AI clusters in the UK**. Not only do such resources enable computationally-focused research collaborations across the UoB campus, but they are essential in national and international projects such as the UK Coronavirus Cancer Monitoring Project. This computational toxicology project (the Fellow and collaborating FSA scientists) will have access to existing IT infrastructure, and will benefit from the architectures being designed for the pursuit of Precision Toxicology (*PrecisionTox*), substantially funded by the European Commission (leveraging a 20M Euro project).

Added value - exceeding the criteria requested by the FSA:

The UoB brings additional dimensions to this proposal, (a) our highly relevant MSc programmes in Bioinformatics and Toxicology, and (b) expertise in legal frameworks for chemical safety - because of our realisation some years ago that changes in chemical risk assessment cannot be driven by science alone. We introduce each of these additional strengths below.

(a) Masters courses in Bioinformatics and Toxicology

The MSc Bioinformatics course - led by [redacted](co-applicant) - was launched in 2017 and has grown rapidly, with 35 students enrolled this year from 221 world-wide applications. Of potential interest to the FSA, this programme is now being expanded to fully 'Distance Learning'. Comprising five taught modules, one group project, and one independent project. This degree provides foundational knowledge and skills in statistics, computer programming and molecular biology. It prepares both wet-bench biologists and clinicians interested in data analysis, as well as statisticians or computer scientists wishing to work in biology, for studies in modern bioinformatics.

Toxicology teaching at UoB has a long and distinguished history, being first established in 1979, and is now the most productive MSc Toxicology course in the UK. Since 2009 alone, we have graduated ca. 250 students, with several alumni now occupying senior positions in industry and academia both in the UK and overseas. Three years ago, the course was focussed around the theme of '*Regulatory science and toxicology for the 21st century*', addressing global challenges in human and environmental health, and further increasing student intake (39 enrolled this year).

These Masters programmes are integrated, with the students coming together for particular components of their training, for example the lectures and workshops focused on the processing and analysis of NAMs/omics data in toxicology.

There are noteworthy benefits that these Masters courses can bring to the proposed FSA/UoB/HSE partnership:

- All students undertake a 10-week research project each summer. This provides an opportunity, annually, for FSA scientists to design and supervise explorative 'pilot projects' in computational toxicology. This could be of particular benefit in years 3 and 4, after the scoping and strategy development activities.
- Each year, many of the top graduates from these courses are recruited directly by our industrial partners. A closer association of the FSA with these Masters degrees would provide a recruitment pool, helping to facilitate the longer term growth of computational toxicology at the FSA.

(b) Law

Risk assessment in the EU mixes hard law (formal legal powers, regulation) with 'soft law' (e.g. technical guidance on risk assessment protocols and protocols for regulatory decision-making). Through the new UoB-led 20M Euro H2020 *PrecisionTox* project, and led by lawyers in the UoB Law School, [redacted]

and [redacted]

we provide soft law provisions that can further explain and mobilise NAMs in chemical risk assessment. Specifically, we will be producing draft guidance and other informational support on the use of NAMs that could be issued by a chemical regulator, and adopted by industry, to fulfil requirements for regulatory compliance. This work will be promoted through targeted expert communications and our national and international networks. While this is one step beyond the computational science that the FSA seeks, we believe that this legal perspective and expertise could be invaluable to the FSA's longer term aspirations.

References:

[redacted]

[redacted]

C: Please provide details of any aspect of the proposed work which are considered innovative in design and/or application? E.g. Introduction of new or significant improved products, services, methods, processes, markets and forms of organisation:

Our approaches are most certainly innovative, in that we are developing risk assessment practices that aim to improve efficiency, reliability and levels of certainty. The focus of our innovation is in *implementing* existing computational tools from, for example, Precision Medicine, to the field of chemical risk assessment. We believe this is the most pragmatic strategy to bring about change in the short to medium term. That is not to imply that UoB (and the supervisory team) are not innovating in new computational algorithms, for example [redacted] and [redacted] - experts in bioinformatics and machine learning - are developing new approaches to process and analyse omics and multi-omics toxicology data, including data-mining technologies, multi-view learning (canonical correlation analysis) and interpretable machine learning (molecular networks).

3. Project plan and deliverables

A: Please provide a detailed project plan including, the tasks and sub-tasks required to realise the objectives (detailed in Part 1). The tasks should be numbered in the same way as the objectives and should be clearly linked to each of the objectives. Please also attach a flow chart illustrating the proposed plan:

Our plan is based on lessons learnt from engaging with ECHA (see Figure 1, above), combining a scoping and strategy development phase (Objective 1), bespoke training (Objective 2), and implementing at least two case studies - the first starting immediately (Objective 3) and a second developed from the scoping phase and starting later in the project (Objective 4). Through the 4-year period, our ambition is to launch a series of additional pilot studies, in particular through our Masters in Bioinformatics and Toxicology degree programmes, to strengthen the basis for a long term partnership with the FSA in computational toxicology. The individual tasks are summarised in a Gantt chart (see separate file).

Objective 1. To deeply scope the FSA's problem space in chemical risk assessment and to (a) map this to our computational NAMs solution space, thereby (b) aiding the FSA to develop a strategy for the utilisation of NAMs, to (c) ultimately provide leadership (i.e., a community hub) by proposing and undertaking inclusive case studies (months 1-24).

Task 1.1 (year 1). Fellow embeds within the FSA Chemical Risk Assessment Team and assimilates knowledge of their current practices and workflows, as well as an understanding of the relevant legislations. Based on our experience working with ECHA, this will be challenging and require extensive background reading by the Fellow. We propose half-day meetings every 2 months, to be held between the FSA, UoB and HSE Science and Research Centre, to present and review the Fellow's progress and understanding of the risk assessment practices, which through year 1 will enable the definition of clear opportunities that could be addressed using computational NAM approaches. Given multiple tasks need to run in parallel during the first year, hence the Fellow will need to distribute their time accordingly, we assign months 1-12 to Task 1.1.

Review R1 (month 6) - Interim review of Fellow's progress by the Project Board (see Section 5 - Project Management), including their understanding of the scientific and regulatory landscape, and communications skills during the monthly meetings.

Review R2 (month 12) - Review of Fellow's progress by the Project Board, including the breadth and depth of scoping data gathered.

Task 1.2 (year 1). Fellow engages with the computational toxicology teams at both UoB and the HSE Science and Research Centre, to increase their knowledge in computational NAMs for chemical risk assessments. The training that the Fellow will need depends on their existing skill set and therefore we cannot predict the precise topics, however by the completion of Task 1.2 they should have a working knowledge of a wide range of NAM approaches, together with specialist expertise in at least one of the key areas of benchmark dosing modelling of molecular data, pathway analysis and/or PBPK modelling. We assign this task to year one, to ensure sufficient time for the Fellow to learn from the collective expertise of the supervisory team. This training will also align strongly with the Fellow's undertaking of Case Study 1 (see Objective 3, below), i.e. the Fellow's training in areas outside of their existing skill set will largely be practically-based, via the case study.

Milestone M1 (by month 12) - Attendance of the Fellow at the 2021 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting, to further strengthen their broader understanding of the roles of NAMs across the international regulatory landscape.

Task 1.3 (year 2). The Fellow and the full supervisory team will build on the discussions in Task 1.1 and map the computational NAM 'solution space' to the FSA's 'problem space' in chemical risk assessment. Overseen by the supervisory team, the Fellow will draft an initial report -

Recommendations for the implementation of New Approaches Methodologies to the FSA's risk assessment of regulated products. The report will include a background and introduction to NAMs, the FSA's problem space identified in Task 1.1, the solution space offered by NAMs, and specific recommendations for one or more new case studies. Again, based on our experience from working with ECHA, this report will require multiple iterations between the FSA and Fellow/supervisory team. We foresee two written outputs from this activity (to be agreed with the FSA): first, a detailed internal report for the FSA focused on introducing NAMs and describing our recommendations for their implementation at the FSA, including proposed case studies; this could be used for various internal purposes such as increasing awareness, contributing to the leadership's strategic planning, etc. in the post-EU exit era. Second, an FSA, UoB, HSE Science and Research Centre multi-authored 'perspective' article, published in a research journal, describing FSA/UoB/HSE's views on the opportunities and challenges of using NAMs for regulatory purposes in chemical risk assessment.

Milestone M2 (month 18) - first draft of *Recommendations for the implementation of New Approaches Methodologies to the FSA's risk assessment of regulated products*

Deliverable 01/01 (month 24) - Internal FSA report - *Recommendations for implementing NAMs into FSA's chemical risk assessment*

Deliverable 01/02 (month 24) - Peer-reviewed research paper - *Opportunities and challenges of using NAMs for regulatory purposes*

Milestone M3 (by month 24) - Attendance of the Fellow at the 2022 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting, to present the opportunities and challenges of using NAMs for regulatory purposes within FSA's practices, for feedback from >50 international regulators.

Objective 2. To ensure that the FSA is trained for the internal use of computational NAMs by delivering in-depth training courses for FSA scientists, including an introduction to existing and emerging NAM technologies, and topics selected from the FSA's NAM strategy (months 1-48).

Task 2.1 (year 1). Develop and deliver a training course to FSA scientists to introduce them to New Approach Methodologies and to help them to consider how NAMs can be of value to the risk assessment of regulated products. The course will be provided by [redacted] and colleagues in their translational toxicology team ([redacted], benefiting from their experience in delivering NAM training to ECHA. The training course is anticipated to last 2 days, covering an introduction to Systems Biology and untargeted molecular assays, lessons learned from Precision Medicine to inform Precision Toxicology, an overview of NAMs and an introduction to how they can be applied to risk assessment, with case studies. Delivery will be face-to-face if Covid restrictions allow, otherwise delivered via video conference.

Deliverable 02/01 (by month 12) - NAM Training Course 1 - Introduction to NAMs for chemical risk assessment

Task 2.2 (year 2). Develop and deliver a training course to FSA scientists to provide a deeper understanding of a particular computational NAM, and how it relates to the FSA's regulatory activities. The topic for this second (and third and fourth) course will be decided through

consultation with the FSA scientists, drawing upon the findings from the scoping activity (Task 1.1) and the development of the FSA's strategy for utilising NAMs (Task 1.3).

Deliverable 02/02 (by month 24) - NAM Training Course 2 - Advanced (topic TBD)

Review R3 (by month 24) - Review format and quality of training course to ensure maximum value of subsequent training courses to the FSA

Task 2.3 (year 3). Develop and deliver a training course to FSA scientists to provide a deeper understanding of a particular computational NAM, and how it relates to the FSA's regulatory activities. Including training in any new tool development.

Deliverable 02/03 (by month 36) - NAM Training Course 3 - Advanced (topic TBD)

Task 2.4 (year 4). Develop and deliver a training course to FSA scientists to provide a deeper understanding of a particular computational NAM, and how it relates to the FSA's regulatory activities. Including training in any new tool development.

Deliverable 02/04 (by month 48) - NAM Training Course 4 - Advanced (topic TBD)

Objective 3. To develop and evaluate confidence in a new hazard assessment workflow that integrates *in vitro* omics toxicity data, benchmark dose modelling and PBPK modelling to serve as the basis for quantitative risk assessment for human health, i.e. towards generating human health-based safety thresholds for FSA and other regulators (months 1-36).

While an ambitious objective, several of the component parts of this proposed hazard assessment workflow - termed Case Study 1 - already exist. Hence the challenges lie more in the assembly of the tools (rather than extensive new algorithm development), determining strategies to assess uncertainty, and trialling the workflow on available datasets.

Critical to this case study is the availability of multi-omics datasets from toxicity studies that employed a high number of dose groups. Until very recently, such datasets did not exist, however we now have available to us a combined metabolomics and transcriptomics dose-response studies with data generated at the US National Toxicology Program and Phenome Centre Birmingham (at UoB). This includes existing rodent liver multi-omics data, and rodent plasma multi-omics data (with substantially more to be collected in Q1-Q2 2021 at Birmingham as part of our framework contract with ECHA). While these data can serve to test the benchmark dose modelling approaches for transcriptomics alone, metabolomics alone, and in combination, in order to test the *in vitro* to *in vivo* extrapolation part of our workflow, we require *in vitro* multi-omics toxicology data. In addition to new *in vitro* (cell line) data being generated in the *PrecisionTox* project, and the potential for further new data through our on-going collaboration (using metabolically competent HepaRG cells) with Professor Maurice Whelan at the JRC, we have sourced some existing metabolomics and transcriptomics data derived from the responses of the HepaRG cell line to a series of liver toxicants (including common drugs).

Task 3.1 (year 1). Investigate and optimise the computational strategies for extracting information from the metabolomics dose-response datasets, i.e. to derive robust and interpretable molecular points of departure (PoD) following exposure of the test system to a chemical. This builds upon related work published using transcriptomics data and Benchmark Dose (BMD) analysis [1] - where the PoDs can be based on individual genes or gene pathways, as well as upon our own recent work (unpublished) in which PoDs are based on individual metabolites. For the greatest confidence in the PoD value (which forms the basis for generating human health-based safety

thresholds), we hypothesise that a combination of upstream transcriptional and downstream metabolic measurements is required in order to provide information on the doses required to both initiate a molecular response and cause a functional biochemical perturbation. We also propose that considering multiple genes and metabolites within the context of molecular pathways will provide the greatest confidence in the PoDs. Concordance between molecular PoD values and those derived from traditional approaches (apical endpoints) - as has been reported [1] - should also provide confidence in these NAMs to regulatory scientists. This approach would also enable molecular pathway-adverse outcome and pathway-disease databases (e.g., Ingenuity Pathway Analysis, MarkerDB [2]) to be interrogated to propose associations between the molecular PoDs and adversity. Such an approach would be more compatible with the current risk assessment philosophy in Europe, based on apical (adverse) outcomes. Indeed, BASF's MetaMap Tox database (comprising metabolomics signatures that are predictive of MoA; [3]) is built around such a similar concept.

Milestone M4 (month 12) - Approaches implemented to enable the derivation of molecular points of departure (PoD), based on metabolomics and transcriptomics data, including an assessment of their concordance with apical endpoint PoD data.

Task 3.2 (years 2-3). Apply biologically-based mathematical models, i.e., PBPK models [4], to extrapolate from *in vitro* multi-omics data (Task 3.1) to *in vivo*, for the purposes of quantitative human risk assessment. Specifically, a computational workflow will be applied - developed by the HSE Science and Research Centre - that integrates PBPK modelling, global sensitivity analysis (GSA), Approximate Bayesian Computation (ABC) and Markov Chain Monte Carlo (MCMC) simulation to facilitate quantitative *in vitro* to *in vivo* extrapolation (QIVIVE). The workflow accounts for PBPK model structure and parameter uncertainty within a computationally efficient framework. This refers to the quality of fit of the model to measured biological monitoring data and a consideration of how this affects an *in vivo* dose response relationship in the context of QIVIVE [5]. This is important as the level of detail (or fidelity) captured in the model could have a bearing on model output [6]. Dependent upon the multi-omics datasets selected for Case Study 1, we will search for molecular (gene, metabolite) measurements from human studies as these would further increase confidence in the framework for *in vitro* to *in vivo* extrapolation if the *in vitro* molecular perturbations had been previously documented in humans. Since the multi-omics HepaRG dataset was derived from the exposure of hepatocytes to common drugs (unpublished, US NTP), measurements in for example human plasma may well already exist.

Understanding and quantifying the level of uncertainty in each step of a chemical safety assessment with NAMs is important for the development of confidence in this approach [7]. This task and case study therefore represents an important step forward to implement the use of NAMs in chemical risk assessment since QIVIVE and reverse dosimetry have been described as the critical "end game" in the workflow of predictive toxicology [8]. QIVIVE is essential in order to transition away from animal model-based toxicology to entirely in vitro/in silico-based toxicological science [8].

Review R4 (month 18) - Review of Fellow's progress in Case Study 1, in particular their understanding of PBPK modelling and how they are managing to work across three sites (HSE Science and Research Centre, FSA and UoB).

Milestone M5 (month 24) - Initial implementation and testing of the QIVIVE workflow.

Deliverable 03/01 (by month 36) - Presentation of findings from Case Study 1 at a toxicology workshop/conference (e.g. 2023 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting).

Deliverable 03/02 (month 36) - Peer-reviewed research paper describing Case Study 1.

Further work by the Fellow on Case Study 1 will be decided based on a discussion with the FSA, UoB and HSE Science and Research Centre, following a review of progress made and, more importantly, the relevant to the FSA.

Objective 4. To develop and deliver a second case study that fortifies the community-wide acceptance of 21st century methods in risk assessments, to accelerate the successful application of NAMs within the FSA (months 25-48).

Task 4 (in years 3-4). The exact nature of this task will evolve over the course of the fellowship and be directed by the detailed analysis of the FSA 'problem space' as well as the NAM 'solution space'. However, it remains possible to define likely courses of action for Objective 4.

The first option is to conduct a new case study that is largely unrelated to Case Study 1. For example, with the UoB supervisory team's expertise in using explainable artificial intelligence (XAI), multi-view learning, and network modelling for the analysis of multi-omics "big" data to tackle challenges in toxicology, we may discover novel opportunities to address FSA challenges in risk assessment. There will need to be consideration of the skillset of the Fellow, as while devoting some time to the training of an early-career scientist is highly appropriate, we cannot jeopardise the primary objective of this fellowship to deliver computational NAMs to the FSA.

Should Case Study 1 be proceeding particularly well, yet some critical additional steps have been identified (e.g. trialling and validation with further datasets), a second option is to focus the Fellow full time on advancing and deploying that hazard assessment workflow in the attempt to generate human health-based safety thresholds for regulators.

An additional option for years 3-4, depending on progress and the availability of relevant molecular data, is to apply the workflow developed in Case Study 1 to a real risk assessment scenario, and to evaluate its relevance and reliability alongside the existing methodologies employed at the FSA.

Milestone M6 (by month 27) - Agreement between FSA, UoB and HSE Science and Research Centre on the focus of Case Study 2 (considering the options presented in the Project Plan)

Review R5 (month 30) - Review of Fellow's progress by the Project Board, specifically their ability to progress Case Study 1 and 2 simultaneously

Deliverable 04/01 (by month 48) - Presentation of findings from Case Study 2 at a toxicology workshop/conference (e.g. 2024 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting)

Deliverable 04/02 (month 48) - Final report describing activities undertaken and outcomes of 4-yr fellowship programme

Ultimately, delivery of this project would make an important first step towards replacing the current slow, inefficient and expensive animal-based risk-assessment process with an animal-free chemical safety assessment process – which would constitute a paradigm shift.

References:

[redacted]

B: Please outline the proposed project milestones and deliverables. Please provide a timetable of key dates or significant events for the project (for example fieldwork dates, dates for provision of research materials, draft and final reporting). Deliverables must be linked to the objectives. We also request some "review points" or "break points" where we can assess the progress of the fellow and ensure we are still receiving good value for money.

Presented in temporary order, per Objective:

	M6	M12	M18	M24	M30	M36	M42	M48
OBJECTIVE 1	R1	R2; M1	M2	D01/01; D01/02; M3				
OBJECTIVE 2		D02/01		D02/02; R3		D02/03		D02/04
OBJECTIVE 3		M4	R4	M5		D03/01; D03/02		
OBJECTIVE 4				M6	R5			D04/01; D04/02

Objective 1

Review R1 (month 6) - Interim review of Fellow's progress by the Project Board (see Section 5 - Project Management), including their understanding of the scientific and regulatory landscape, and communications skills during the monthly meetings.

Review R2 (month 12) - Review of Fellow's progress by the Project Board, including the breadth and depth of scoping data gathered.

Milestone M1 (by month 12) - Attendance of the Fellow at the 2021 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting, to further strengthen their broader understanding of the roles of NAMs across the international regulatory landscape.

Milestone M2 (month 18) - first draft of *Recommendations for the implementation of New Approaches Methodologies to the FSA's risk assessment of regulated products*

Deliverable 01/01 (month 24) - Internal FSA report - *Recommendations for implementing NAMs into FSA's chemical risk assessment*

Deliverable 01/02 (month 24) - Peer-reviewed research paper - *Opportunities and challenges of using NAMs for regulatory purposes*

Milestone M3 (by month 24) - Attendance of the Fellow at the 2022 Accelerating the Pace of Chemical Risk Assessment (ACPRA) annual meeting, to present the opportunities and challenges of using NAMs for regulatory purposes within FSA's practices, for feedback from >50 international regulators.

Objective 2

Deliverable 02/01 (by month 12) - NAM Training Course 1 - Introduction to NAMs for chemical risk assessment

Deliverable 02/02 (by month 24) - NAM Training Course 2 - Advanced (topic TBD)

Review R3 (by month 24) - Review format and quality of training course to ensure maximum value of subsequent training courses to the FSA

Deliverable 02/03 (by month 36) - NAM Training Course 3 - Advanced (topic TBD)

Deliverable 02/04 (by month 48) - NAM Training Course 4 - Advanced (topic TBD)

Objective 3

Milestone M4 (month 12) - Approaches implemented to enable the derivation of molecular points of departure (PoD), based on metabolomics and transcriptomics data, including an assessment of their concordance with apical endpoint PoD data

Review R4 (month 18) - Review of Fellow's progress in Case Study 1, in particular their understanding of PBPK modelling and how they are managing to work across three sites (HSE Science and Research Centre, FSA and UoB).

Milestone M5 (month 24) - Initial implementation and testing of the QIVIVE workflow.

Deliverable 03/01 (by month 36) - Presentation of findings from Case Study 1 at a toxicology workshop/conference (e.g. APCRA 2023)

Deliverable 03/02 (month 36) - Peer-reviewed research paper describing Case Study 1

Objective 4

Milestone M6 (by month 27) - Agreement between FSA, UoB and HSE Science and Research Centre on the focus of Case Study 2 (considering the options presented in the Project Plan)

Review R5 (month 30) - Review of Fellow's progress by the Project Board, specifically their ability to progress Case Study 1 and 2 simultaneously

Deliverable 04/01 (by month 48) - Presentation of findings from Case Study 2 at a toxicology workshop/conference (e.g. APCRA 2024)

Deliverable 04/02 (month 48) - Final report describing activities undertaken and outcomes of 4-yr fellowship programme

4. Organisational experience, expertise and staff effort

A: Please provide evidence of up to three similar fellowships that the project lead applicant and/or members of the project team are currently undertaking or have recently completed.

Project 1 - MEtabolomics standaRds Initiative in Toxicology (MERIT): developing best-practice guidelines and minimal reporting standards for the acquisition, processing and analysis of metabolomics data [redacted]

Start date: April 2017

End date: November 2018

Client who commissioned (funded) the project: **European Centre for the Ecotoxicology and Toxicology of Chemicals (ECETOC)**

Collaborative partners and their contribution: **University of Birmingham (co-lead)**, Imperial College London (co-lead), with multiple partners contributing expert knowledge in NAMs, metabolomics, regulatory toxicology - including BASF, European Food Safety Authority, Health and Safety Executive, International Agency for Research on Cancer, Syngenta, The Francis Crick Institute, Unilever, University of Oxford, US Food & Drug Administration, US Environmental Protection Agency, Vrije Universiteit Amsterdam.

Value: [redacted]

Work conducted: (1) Developed best practice guidelines to facilitate the harmonisation of laboratory protocols for the acquisition, processing and computational analysis of metabolomics data; (2) Developed minimal reporting standards for metabolomics applied to regulatory toxicology including the use of rigorous QA/QC; (3) Designed a metabolomics ring-trial (laboratory intercomparison) around a toxicology case study that ultimately would quantify reproducibility in technical measurement, data analysis and inference of biological knowledge, in part to identify the most problematic steps in the metabolomics workflow for further refinement.

How this demonstrates the relevant skills and/or expertise: The technical and leadership skills required (by Viant) to deliver this project were demonstrated by (a) all objectives being met, (b) a paper published in the high impact journal *Nature Communications* - titled 'Use cases, best practice and reporting standards for metabolomics in regulatory toxicology' ([redacted] (d) the reporting standards helped to launch the formal definition of a reporting framework for metabolomics (OECD Metabolomics Reporting Framework, PI: Viant).

What skills the team used to ensure success: expert knowledge, discipline and collegiality.

Project 2 - Services related to metabolomics measurements and multi-omics data interpretation

Start date: December 2018 (4-yr framework, on-going)

Client who commissioned (funded) the project: **European Chemical Agency**

Collaborative partners and their contribution: **University of Birmingham & University of Birmingham Enterprise** (commercial arm of UoB) - expertise in NAMs, omics technologies, computational toxicology

Value: [redacted]

Work conducted: 7 projects to date, ranging from consultation on the application of NAMs to chemical risk assessment (e.g. consultancy report titled - *Analysis of the applicability of NAMs to support environmental hazard assessment and priority setting of industrial chemicals*), multi-omics and computational approaches to chemical grouping, and - of particular relevance to this proposal - the application of multi-omics and computational approaches to benchmark dosing and deriving molecular points of departure, also the delivery of multiple training courses in NAMs to ECHA.

How this demonstrates the relevant skills and/or expertise: Winning this competitive tender with the European Chemicals Agency demonstrates that our application was leading amongst all the European offerings.

What skills the team used to ensure success: expert knowledge, thinking outside-of-the-box, commitment and collegiality.

Project 3 - Toward Precision Toxicology: New Approach Methodologies for Chemical Safety (PrecisionTox)

Start date: Feb 2021 (5-yr project)

Client who commissioned (funded) the project: **European Commission H2020 programme**

Collaborative partners and their contribution: **University of Birmingham (lead)**, University of Heidelberg, Indiana University, Karlsruher Institut für Technologie, Fundacio Centre de Regulacio Genomics, WatchFrog SA, Clemson University, University of Oxford, US National Institute of Diabetes and Digestive and Kidney Diseases, US National Institutes of Health, Helmholtz Zentrum für Umweltforschung, AlterTox AXA, Cell Networks GmbH, Michabo Health Science Ltd, Acondicionamiento Tarrasense Associacion LEITAT, Misvik Biology Oy.

Value: [redacted]

Work conducted: The overarching goal of *PrecisionTox* is to establish a new, 3Rs-compliant, cost-effective testing paradigm for chemical safety assessment — Precision Toxicology — that revolutionizes regulatory toxicology, replaces animal testing, reduces uncertainty, and determines safety factors in assessing risks to human health. We accomplish this goal by identifying molecular key event (KE) biomarkers, predictive of chemically induced adverse health effects in humans, that feed directly into regulatory and industry practice via the systematic use of distantly related animal species from across the tree of life and the highly interdisciplinary mix of genomics, metabolomics, evolutionary theory, quantitative genetics, data science, toxicology, and law. Objectives include:

- Biomarker Discovery, Data Commons, and NAM Toolbox: Provide comprehensive data management, data integration, and data dissemination; identify candidate molecular mechanisms predictive of human toxicity; and incorporate these into a final NAM based hazard prediction tool.
- Causation and Sources of Variation: Evaluate the degree of certainty in causal links between molecular KEs and chemical risks to human health, and deliver new approaches

that determine cell/organ-specific and human susceptibilities given a known genetic background, providing reliable data-driven statistical estimates of safe exposure limits for humans that account for variation.

- Regulatory Analysis and Application: Identify opportunities for assimilation of new approach methodologies within existing regulatory structures and produce, directly with chemical regulators, and develop guidance for the use and reporting of Precision Toxicology by industry for regulatory compliance.

In summary, this project is designed to significantly advance the fundamental science of Precision Toxicology. Its aim is to translate discoveries into new approach methodologies that are more reliable than animal testing and have a measureable impact on human health through implementation in regulatory safety assessments of chemicals - and hence strongly aligned with the FSA ambitions.

How this demonstrates the relevant skills and/or expertise: Winning a 20M Euro award from the European Commission demonstrates the excellence of our team, led by UoB.

B: For the proposed Fellow and Supervisor please list:- the names and grades with details of their specialism and expertise, their role in the project and details of up to 4 of their most recent, relevant published peer reviewed papers (where applicable). If new staff will be hired to deliver the project, please detail their grade, area/(s) of specialism and their role in the project team.

Lead Applicant/Fellow and organisation, details of specialism and expertise:

Other named staff/Supervisor, details of specialism and expertise (Principle Investigators name and details first):

Primary supervisor: [redacted] **(professorial grade 10), University of Birmingham**

[redacted] is Professor of Metabolomics (leading the Metabolomics & Systems Toxicology Laboratory), Executive Director of Phenome Centre Birmingham (UoB's £8M research centre in metabolomics), and a past President of the International Metabolomics Society. His research focuses on developing New Approach Methodologies, in particular omics and computational approaches, in the fields of human and environmental toxicology. [redacted] scientific mission includes *implementing* novel molecular mechanistic solutions in chemical safety science for industry and regulators. He has co-authored over 180 publications and his work has been recognised by the Joseph Chamberlain Award for Excellence in Academic Advancement (2013; UoB's highest award for academic achievement) and a 2015 Lifetime Honorary Fellowship of the International Metabolomics Society.

Specialism and expertise: analytical and computational metabolomics applied to toxicology, toxicokinetics, chemical grouping/read-across, benchmark dose modelling, reporting standards, NAMs applied to regulatory toxicology

Role in the project: Principal supervisor

Publications:

RV D'Elia, SA Goodchild, CL Winder, AD Southam, RJM Weber, FM Stahl, C Docx, V Patel, AC Green, [redacted] RA Lukaszewski, WB Dunn, Multiple metabolic pathways are predictive of ricin intoxication in a rat model, *Metabolomics* 15, Article number 102 (2019).

[redacted] TMD Ebbels, RD Beger, DR Ekman, DJT Epps, H Kamp, PEG Leonards, GD Loizou, JI MacRae, B van Ravenzwaay, P Rocca-Serra, RM Salek, T Walk, RJM Weber, Use cases, best practice and reporting standards for metabolomics in regulatory toxicology, *Nature Communications* 10, Article number 3041 (2019).

NS Taylor, A Gavin, [redacted] Metabolomics discovers early-response metabolic biomarkers that can predict chronic reproductive fitness in individual *D. magna*. *Metabolites* 8, 42 (2018).

CS Dekkers, TD Williams, J Zhang, J Zhou, RJ Vandebriel, LJJ De La Fonteyne, ER Gremmer, S He, EJ Guggenheim, I Lynch, FR Cassee, WH De Jonga, [redacted] Multi-omics approaches confirm metal ions mediate the main toxicological pathways of metal-bearing nanoparticles in lung epithelial A549 cells. *Environmental Science: Nano* 5, 1506-17 (2018).

Supervisory team: [redacted] **Lead of *PrecisionTox*, University of Birmingham**

[redacted] is Chair of Environmental Genomics (School of Biosciences), co-founder of the *(i)* Environment Care Consortium (ECC), the *(ii)* Solve Pollution Network (SPN) and *(iii)* Michabo Health Science. He is a Fellow of the Royal Society of Biology and a recipient of the Royal Society Wolfson Research Merit Award. He is also the Project Coordinator of a recently awarded €20 million project by the European Union called *PrecisionTox* to transform environmental health protection by new approach methodologies using omics technologies and model systems that improve certainty in the causal associations between exposure to hazardous compounds and adversity to health.

Specialism and expertise: Genome sequencing and functional genomics; comparative genomics for cross-species extrapolation; environmental health; new approach methodologies (NAMs).

Publications:

[redacted]

Supervisory team: [redacted] **Director of Centre for Computational Biology, University of Birmingham**

[redacted] is Chair of Bioinformatics, founder and director of the Centre for Computational Biology. He is the Alan Turing Institute Theme lead for Data Intensive Life Sciences for the

University of Birmingham and holds a Turing Fellowship in Population Diversity at Varying Scales. He is the founder and chair of the executive committee of the Compute and Storage for Life Sciences initiative. He will provide supervision and access to expertise in data science applied to the life sciences.

Specialism and expertise: Trained in Applied Mathematics, [redacted] has been working in Data Science applied to the Life Sciences for more than 20 years focusing on Population Diversity, Precision Medicine, Cancer Genomics and System Biology. He has been applying, as well as developing, cutting-edge methods to impact on a broad range of applications and health conditions, currently focusing on eXplainable AI approaches. Subsequently, he has been increasingly involved in leadership roles to conceive, establish and lead new local and international initiatives in Data Science for Life Sciences in both Industry and Academia.

Publications:

Lee L*, [redacted] Starkey T, Turnbull CD; UK Coronavirus Cancer Monitoring Project Team, Kerr R, Middleton G. (2020) COVID-19 mortality in hospitalized cancer patients is not significantly affected by chemotherapy or other anti-cancer treatments. *Lancet.* 395(10241):1919-1926.

[redacted] Kaisaki, P. J., Argoud, K., Blaise, B. J., Veselkov, K., Ebbels, T. M., Tsang, T., Wang, Y., Bihoreau, M. T., Mitchell, S. C., Holmes, E. C., Lindon, J. C., Scott, J., Nicholson, J. K., Dumas, M. E. and Gauguier, D. (2012) Untargeted Metabolome Quantitative Trait Locus Mapping Associates Variation in Urine Glycerate to Mutant Glycerate Kinase. *Journal of Proteome Research*, 11:631–642.

[redacted] Mainzer- Sergeevna, Weihao G, L, Jurauskienė J, Madak-Erdogan Z. 2020 Health Disparities Research is Enabled by Data Diversity but Requires Much Tighter Integration of Collaborative Efforts. *Journal of Global Health*. *JOGH (2020); Oct 10: 020351*.

Hedjazi L, Dumas M, Gauguier D, Zalloua P, Nicholson J, Dumas ME, [redacted] (2014) mQTL-NMR: an integrated suite for genetic mapping of quantitative variations of 1H NMR-based metabolic profiles. *Analytical Chemistry* 87(8):4377-84.

Supervisory team: [redacted] **Head of Computational Toxicology, Health and Safety Executive Science and Research Centre**

Specialism and expertise: [redacted] is a computational toxicologist with over 35 years' experience in quantitative, mechanistic, chemical toxicology. For the past 22 years [redacted] has been engaged in strategic research for the Health & Safety Executive (HSE) and external customers investigating whether computational tools can be designed to exploit new technologies and mathematical modelling to provide a biologically based, quantitative chemical risk assessment. This work has focused on the use of PBPK modelling to analyse, quantify and explain toxicological data with the ultimate aim of replacing the current slow, inefficient and expensive animal-based chemical risk assessment paradigm. For the past four years [redacted] has also been investigating developments in personalised medicine where data obtained in people may potentially be appropriate for occupational and environmental toxicology. The use of gene expression (transcriptomics), metabolite (metabolomics) data and bioinformatics could lead to the development of a 'next generation' approach to chemical risk assessment based on human data.

Publications:

[redacted]

[redacted]

Supervisory team: [redacted] **University of Birmingham**

Specialism and expertise: [redacted] is a Lecturer in the School of Biosciences and in the Centre for Computational Biology. He is an expert at computer programming and in the design and implementation of algorithms that deliver explainable artificial intelligence (XAI), multi-view learning, and network modelling for the analysis of multi-omics "big" data to tackle the emerging data science challenges in environmental and toxicological research. Unlike standard machine and deep learning methods, which are often faulted for producing a “black box” with no knowledge provided on the data combinations used to derive the outputs, [redacted] research makes the [redacted] decisions easy to follow and are thus “explainable”.

Publications:

[redacted]

Supervisory team: [redacted] **Director of Bioinformatics - Phenome Centre Birmingham, University of Birmingham**

Specialism and expertise: [redacted] has over a decade of expertise in bioinformatics, data science and computational metabolomics, and his reputation led to accolades such as a current Director of the International Metabolomics Society and a member of the ELIXIR-UK ([redacted]Management Committee. His research team's interests include the development and application of data processing, biostatistics and data mining tools to facilitate biochemical annotation and interpretation of clinical and toxicological metabolomics data. He is a strong supporter of standardisation across the field of metabolomics and life sciences, from the reporting of experimental data (i.e. findable, accessible interoperable and reusable - FAIR) and metadata, through to the use of easily accessible and reproducible computational workflows.

Publications:

[redacted]

Postdoctoral Fellow: to be appointed (grade 7, spine point 30)

Specialism and expertise: we will recruit a specialist in computational toxicology

5. Project management

Please fully describe how the project will be managed to ensure that objectives and deliverables will be achieved on time and on budget. Please describe how different organisations/staff will interact to deliver the desired outcomes.

Highlight any in-house or external accreditation for the project management system and how this relates to this project:

The structure, roles and responsibilities will be:

Project Board – made up of the Project Management Team ([redacted] see below), the FSA lead, and [redacted] The role of the board is to guide the research, providing collective and unified direction. They will ensure the project is on track (in terms of milestones and deliverables), that resources (financial and staff) are being used appropriately, perform effective decision making and risk management, and ensure the terms of the contract are met. They will check and verify the developing research is fit for purpose, reliable, robust and applicable.

Project Management Team – consists of Professors [redacted], with overall project management responsibility lying with [redacted] This team will run the project on a day-to-day basis, supervising the new fellow, directing and leading the scoping and implementation phases, and overseeing (and contributing to) the writing of all reports. This team will be responsible for ensuring the project plan is feasible and realistic, committing resources from UoB are needed, ensuring the quality of deliverables and the integrity of the project.

UoB's 'People and Organisational Development' (POD) unit offers a range of training courses to support the development of the new fellow. They will be required to take the course 'Project Management Principles' to ensure they understand the expectations of the supervisory team as well as to improve their own skill set.

The UoB Project Management Team is open to FSA input on project management, should the FSA have any particular requirements for this project.

6. Risk management

Below, please identify all relevant risks in delivering this project on time and to budget. Briefly outline what steps will be taken to minimise these risks and how they will be managed by the project team:

The risks and their management are presented in temporal order, from recruitment through Objectives 1-4, along with some general risks.

Recruitment:

Risk 1: Delays to recruiting the Fellow either due to the bureaucratic processes involved, or because the applicant pool is below the standard required, or both, ultimately risking a delay to the project.

Management of risk 1: Since the training provided to the FSA in NAMs (Objective 2) does not depend on recruitment of the Fellow, this part of the project can begin at a convenient time for the FSA. This will allow a part of the overall project to begin immediately. If recruitment delays were considered to be of high negative impact by the Project Board, we could explore sub-contracting part of Task 1.1 (the scoping) to a member of our existing team in the University of Birmingham Enterprise (as a short term appointment) to allow the scoping to begin while the Fellow is recruited.

Objective 1

Risk 2: This ambitious project requires a Fellow with a strong computational toxicology background and a significant interest in translating that knowledge to regulatory science. We may discover the Fellow's knowledge is balanced more towards the computational, and/or is focused deeply in one aspect of computational toxicology and hence lacking a broader perspective required for Objective 1.

Management of risk 2: We propose two early reviews, at 6 and 12 months, to ensure the Fellow receives the support and training required for them to co-deliver the Objective 1 deliverables at the end of year 2.

Risk 3: The academic team will present ideas and recommendations that are too 'blue skies' for the Regulated Products Risk Assessment Team.

Management of risk 3: We will maintain a continual dialogue between all the parties involved, not be afraid to ask (and re-ask) any questions, and draw upon our experience of working directly with regulators at ECHA to ensure the NAM implementation plan is fit for purpose.

Objective 2

Risk 4: The training courses are delivered at the wrong level.

Management of risk 4: We won't develop any of the courses, including the introduction to NAMs course, until we have an improved understanding of the level of knowledge of the FSA scientists who will receive the training. The course material will be prepared accordingly. After each course we will circulate a short survey for feedback from each attendee. In addition, we have introduced a formal review (R3, by month 24) to obtain more extensive feedback on the format, level, contents etc. of the courses, at a midpoint of the 4-yr programme.

Objective 3

Risk 5: While we have extensive knowledge of available datasets and relevant databases/knowledge bases, we may discover that some new experimental data will be beneficial to Case Study 1 (or 2).

Management of risk 5: Depending on the scale of data generation, we could attempt to source the data through our existing networks and facilities, or if the data generation aligns with another project (e.g. H2020 *PrecisionTox*) we might be able to generate it anew, or seek additional external funding to enable that data generation.

Risk 6: Conducting Objectives 1 and 3 in parallel may be challenging for the Fellow, if they are not sufficiently experienced in multi-tasking, limiting progress with both activities.

Management of risk 6: We could structure year 1 and 2 into multi-month blocks, allowing the Fellow to focus on one principal activity at any one time. Furthermore the supervisory team commits to increasing their support of the Fellow should they struggle with a particular computational NAM. We have built in a formal review (R4, at month 18) to ensure the Fellow is coping with working across 3 sites, following the introduction of the PBPK modelling component in Objective 3 by the HSE Science and Research Centre.

Risk 7: The implementation of a NAM-based hazard assessment workflow, utilising molecular mechanistic (omics) data, benchmark dose analysis and QIVIVE, requires more time than allocated in the Gantt chart.

Management of risk 7: If Case Study 1 is of particularly high value to the FSA, and the progress during years 1-3 is very promising, the Project Board may conclude the Fellow should remain fully focused on Case Study 1 (not 2) until the end of the 4-yr programme.

Objective 4

Risk 8: The Project Board is unable to prioritise a single case study from Objective 1 to take forward as Case Study 2.

Management of risk 8: External input can be sought from our networks of scientists working in regulatory applications of NAMs to help guide the selection. Furthermore, there is the potential to take forward a number of ideas from the strategy development phase through Masters research projects.

General

Risk 9: While accurate budgeting has been completed during the planning phase, deviations are noted during the course of the project.

Management of risk 9: Given that the total budget is dominated by staff costs, under or over-expenditure are very unlikely to occur. Expenditure will be monitored by the UoB supervisory team.

Risk 10: On-going lockdowns through 2021 and beyond.

Management of risk 10: UoB has invested in robust software to support virtual meetings, and the Fellow will have access to their own institutional Zoom account, alongside a high-quality researcher laptop, to ensure that high quality communication and effective working is maintained over the duration of the project, no matter the threat from the pandemic.

7. Quality management

A: Please provide details of the measures that will be taken to manage and assure the quality of work. You should upload your Quality Assurance policy in the supporting documents section of your application.

This should include information on the quality assurance (QA) systems, which have been implemented or are planned, and should be appropriate to the work concerned. All QA systems and procedures should be clear and auditable and may include compliance with internationally accepted quality standards specified in the ITT e.g. ISO 9001 and ISO17025.

Specific to science projects and where relevant, applicants must indicate whether they would comply with the Joint Code of Practice for Research (JCoPR). If applicants do not already fully comply with the JCoPR please provide a statement to this effect to provide an explanation of how these requirements will be met. The FSA reserves the right to audit projects against the code and other quality standards.

The lead principle investigator is responsible for all work carried out in the project (including work supplied by sub-contractors) and should therefore ensure that the project is carried out in accordance with the Joint Code of Practice.

Model validation and QA/QC need to be undertaken (at a minimum of the requirements of the FSA (MSRO checklist)) as part of the project.

The quality assurance considerations need to include how the work will meet the standards in the Aqua Book:

The University of Birmingham's **Code of Practice for Research** (last updated March 2020) defines the University's policies and expectations in relation to the conduct of research under its auspices. The University is committed to research excellence and to the rigorous pursuit of new knowledge. As such it is committed to maintaining the highest standards of scholarly and scientific integrity in its research. It expects all Researchers to work to these standards.

Where research falls within specific regulatory and legislative frameworks (e.g. the UK Policy Framework for Health and Social Care, the Human Tissue Act 2004, the Medicines for Human Use (Clinical Trials) Regulations 2005, or the Animals (Scientific Procedures) Act 1986), researchers are required to comply with the relevant regulatory requirements and the University's specific ethics and governance processes managed by specialist committees which report into the Research Governance Ethics and Integrity Committee. However, no such regulatory and legislative frameworks apply to this computational project.

Researchers must comply with the University's **Policy on Research Data Management** (RDM), which provides more detailed guidance on this matter and definitions of Research Data and Open Data. Its formulation was guided by key aspects of the Concordat on Open Research Data, as produced by HEFCE, JISC, RCUK, UUK and Wellcome, which sets a framework for best practice within UK HEIs with respect to the management of all research data.

With regards to training, the University of Birmingham's quality management system is BIQAES (Birmingham Integrated Quality Assurance and Enhancement System). BIQAES encompasses the key processes which the University has put in place to monitor, review and enhance academic standards, the quality of its learning, teaching and assessment and the academic support given to students. It is informed by the Quality Assurance Agency's (QAA's) Academic Infrastructure, which comprises the Code of Practice for the Assurance of Academic Quality and Standards in Higher Education, Framework for Higher Education Qualifications, Subject Benchmark Statements and Programme Specifications.

The Joint Code of Practice for Research (JCoPR) is not specifically named within the University of Birmingham's 'Codes of Practice, Policies and Guidance' documentation. However the JCoPR and the University of Birmingham's Code of Practice for Research (UoB CoPR) share common elements:

- Responsibilities and Competence (JCoPR) maps to Integrity and Accountability (UoB CoPR);
- Project planning (JCoPR) encompasses Ethics review and Research involving animals (UoB CoPR); also the University of Birmingham's Code of Ethics states that "Responsible ethical conduct is expected in all aspects of research, including applying for funding, experimental design, generating and analysing data, using equipment and facilities, publishing results and acknowledging the direct and indirect contribution of colleagues, collaborators and others.", mapping onto Quality control and Facilities and equipment (JCoPR);
- Handling of samples and materials (JCoPR) maps to Research involving controlled items and Security-sensitive research material (UoB CoPR);
- Documentation of procedures and methods and Research / work records (JCoPR) maps to Research Data and Publications (UoB CoPR);

- Health and safety (JCoPR) is covered by the University of Birmingham's Health and Safety Policy;
- In addition the UoB CoPR covers Intellectual Property, Conflicts of Interest, Adverse Events and Misconduct.

B: Please identify the key ethical issues for this project and how these will be managed. Please respond to any issues raised in the Specification document and please describe the ethical issues of any involvement of people, human samples, animal research or personal data in this part. In addition, please describe the ethical review and governance arrangements that would apply to the work done.

Applicants are reminded that, where appropriate, the need to obtain clearance for the proposed project from their local ethics committee. This is the responsibility of the project Lead Applicant. However, if a sub-contractor requires such clearance the project Lead Applicant should ensure that all relevant procedures have been followed. If there are no ethical issues please state this:

There are no ethical issues associated with this project. In particular, the proposed research does not involve people, human samples, animal research or personal data. Existing toxicological datasets derived from animal studies may be analysed.

C: Please identify any specific data protection issues for this project and how these will be managed. Please respond to any specific issues raised in the Specification document. Please note that the successful Applicant will be expected to comply with the Data Protection Act (DPA) 2018 and ensure that any information collected, processed and transferred on behalf of the FSA, will be held and transferred securely.

In this part please provide details of the practices and systems which are in place for handling data securely including transmission between the field and head office and then to the FSA. Plans for how data will be deposited (i.e. within a community or institutional database/archive) and/or procedures for the destruction of physical and system data should also be included in this part (this is particularly relevant for survey data and personal data collected from clinical research trials). The project Lead Applicant will be responsible for ensuring that they and any sub-contractor who processes or handles information on behalf of the FSA are conducted securely. Any proprietary data used in development of the system will remain confidential and will be shared with the contractor in confidence and only with permission of the data owners. Your response should include, but should not be limited to facilities and measures:

- to ensure ongoing confidentiality, integrity, availability and resilience of processing systems and services;

- to comply with the rights of data subjects in respect of receiving privacy information, and access, rectification, deletion and portability of personal data;
- to ensure that any consent-based processing meets standards of active, informed consent, and that such consents are recorded and auditable;
- to ensure legal safeguards are in place to legitimise transfers of personal data outside the EU (if such transfers will take place);
- to maintain records of personal data processing activities; and
- to regularly test, assess and evaluate the effectiveness of the above measures.

As defined in the University of Birmingham's **Data Protection policy:**

This Policy has been approved by the University's Executive Board and sets out the University's requirements as Data Controller when processing Personal Data.

It applies to all types of Personal Data, including Special Category Data, and hence includes any activity involving Personal Data, such as collecting, analysing, sharing, transferring, storing or deleting data in any media or format. This includes electronic Personal Data, photographic, video or audio Personal Data, and Personal Data in the form of human tissue samples, biometric or genomic data and paper records. It also applies whether we collect the information from individuals, whether it is provided to us by those individuals or other people or whether it is collected from other sources.

All staff, students, honorary and associate members of staff and any other University of Birmingham Data Users must comply with this Policy, and disciplinary action can be taken against those who do not comply, particularly in cases when there has been deliberate, wilful or negligent disregard of the Policy and University requirements.

The University has appointed a Data Protection Officer to advise the University on data protection law, monitor compliance, provide advice to Data Users, and ensure that guidance, training and resources are available to Data Users.

All staff must complete the University's Baseline Data Protection Training,

Six data protection principles must be followed: 1. Lawfulness and fairness; 2. Purpose Limitation; 3. Data minimisation; 4. Accuracy; 5. Storage limitation; and 6. Security.

As defined in the University of Birmingham's **Policy on Research Data Management:**

Research Data should be managed to the highest agreed standards, in accordance with funder requirements, current legislation, including Data Protection legislation, University IT Security policies and standards throughout the Research Data lifecycle as part of the University's commitment to research excellence.

Other related **University of Birmingham IT policy and procedures** include:

(i) General Conditions of Use of Computing and Network Facilities,

(ii) Information Security and Management Policy,

(iii) Software Licencing Policy,

(iv) Guest Wireless Network Acceptable Use Policy.

Data storage: Toxicology data can be stored on the University of Birmingham (UoB) storage (BEAR Research Data Store), accessed via network shares mounted on the computers of the Principal Investigator (PI), Co-PI's and other researchers. Backups are made overnight from the Research Data Store (RDS) and any files that are created or changed that day will be backed up. Backups are also copied to a second location for disaster recovery purposes. Access to the data is restricted to those who have been granted access to the project by the PI and they must have a UoB username and password which can be provided for collaborating researchers. Data can only be accessed off campus through use of the 2-factor authentication remote access service (VPN). Data storage of up to 3TB is provided free of charge to any given project.

Data Sharing: For data sharing between project participants (without the need for a UoB username and password), the UoB provides its own free file sync and share solution similar to Dropbox called BEAR DataShare, with the main benefit being that the data is stored on campus, in the same location as the RDS. BEAR DataShare allows UoB research staff to securely share files with external collaborators and sync data (up to 25GB) between different devices. External users (non-UoB) of BEAR DataShare can also upload data if given appropriate permissions. BEAR DataShare is provided free of charge for UoB researchers and their collaborators.

For the sharing of data with the general public, experimental data that underpins published work will be deposited in trusted digital repositories. To that end, UoB uses PURE which is the UoB's research information and management system; this gathers research outputs and data in a central database. PURE is designed to store and integrate information on research activity in a structured and standardised way. When research data is uploaded to PURE, the associated metadata is created automatically and PURE can act as a repository for smaller data files (an example being text files that contain numerical information). Members of academic staff have PURE accounts and can update and add to their research profiles.

If there is a requirement to transfer multi-TB data sets then our BEAR Globus service can transfer data quickly to and from the Research Data Store. The data transfer is usually controlled using the Globus web service which automatically manages background data transfers to be completed. The BEAR Globus endpoint is directly connected to both the Research Data Store storage facilities Globus is used in a number of large international scientific organisations, for example ORNL, CERN, Sanger, Crick, Archer (RDF) and so is well suited for large inter-institutional data transfers.

When a paper is published as a result of this research, the data that underpins it will be stored securely in the research data archive for at least 10 years (if this is not already done so within an external trusted digital repository such as a funders or journal repository). Discovery of the data will be enabled when the data location is added to the UBiRA system; this will be done via the web portal [redacted] which in turn is scoured by Google thus making it public. There is a workflow in place on how the data can be accessed.

Timeframes for data release: The UoB pledges to release all experimental data that underpins published work. In compliance with RCUK's policies, all published work will be open access and UoB will release all underpinning experimental data at the point of publication. This will either be at the time a journal publishes a preprint of a paper online or at which time UoB publishes work itself; otherwise, there is no requirement for the UoB to set a specific embargo period on the release of such data. The UoB will ensure that the experimental data is in a non-proprietary, open

format at the point of release. However, UoB acknowledges that some intellectual property may be generated during the course of the research project; in this instance, the data may be embargoed for such time as deemed necessary.

Data Archive: Data which is associated with the research project which is not used to support a publication will be archived in accordance with University of Birmingham research governance processes in the secure UoB BEAR Archive. It will be archived for a period of time in line with the UoB Research Data Management Policy (with the minimum period agreed at the point of archiving with the PI) and will only be accessible upon an application for restoration by an appropriate person such as the PI.

Data Disposal: The data will then be disposed of from the UoB Shared drives /Archive after the appropriate retention time, this will also include deletion from storage servers and backup tapes (described in the UoB Backup & Retention Policy). If earlier deletion is required then the PI or their proxy will need to send in a Service Desk ticket to IT Services to initiate deletion. All data will be deleted apart from; metadata that surrounds the file, name, size, creation date and deletion date, but no contents of the data will be stored.

D: The Food Standards Agency is committed to improving sustainability in the management of operations. Procurement looks to its suppliers to help achieve this goal. You will need to demonstrate your approach to sustainability, in particular how you will apply it to this project taking into account economic, environmental and social aspects. This will be considered as part of our selection process and you must include your organisations sustainability policies in your application.

Please state what (if any) environmental certification you hold or briefly describe your current Environmental Management System (EMS).

Ultimately, the established tool needs to be of value beyond the life of the fellowship and aid in risk assessment long term. Before completion of the fellowship, members of the FSA will need to have been fully trained in the use of the developed tool(s):

As long ago as 2007, a Higher Education Funding Council review identified the University as 'getting really serious' about sustainability, and progress has continued since then. The University makes a significant contribution to sustainable development, not only in its role as an internationally recognised provider of research and teaching, but also in the way it performs as a business and engages positively with the local and wider community.

The University of Birmingham has both a **Sustainability policy** (updated 2018), and a **Sustainable procurement policy** (updated August 2020).

The key areas through which sustainability is approached include:

1. Education, research and knowledge transfer - increasing awareness, understanding and ensuring high standards of sustainability behaviour by staff and students. Serving society by producing and promoting research and teaching on sustainability.
2. Energy and carbon management.
3. Emissions and discharges.
4. Waste and material resources.
5. Water.

6. Transport.

7. Buildings.

8. Biodiversity.

9. Procurement – encouraging systems thinking and applying the principles of the circular economy by embedding sustainable, ethical and life cycle considerations in purchasing decisions.

10. Community.

11. Wellbeing.

12. Adapting for climate change.

Software sustainability: Computational tools, workflows and data resources developed as part of the project will be open source and hosted on GitHub. GitHub is a code hosting platform for version control and collaboration. It will ensure that project partners and external collaborators have the ability to openly contribute during and/or after the project (i.e. further development and maintenance).

We have demonstrated previously (and continue to) a long-term commitment to computational metabolomics and toxicology, data standards and software interoperability. For example, UoB are tightly connected with [redacted] and are part of the national node, providing long term sustainability of tools and databases of general interest, including interoperability with additional tools and databases.
Additionally, UoB provides a range of software related services to UoB researchers, and research groups, with the aim of improving the research software written and used by the researchers. Where needed we will make use of these services to ensure the sustainability of the software and resources developed as part of this project.

E: Where applicable please indicate how you intend to disseminate the results of this project, including written and verbal communication routes if appropriate. Applicants are advised to think carefully about how their research aligns with the FSA strategy, what is the impact that their research has on public health/ consumers and decide how the results can best be communicated to the relevant and appropriate people and organisations in as cost-effective manner as possible. Please provide as much detail as possible on what will be delivered. Any costs associated with this must be documented in the Financial Template.

The applicant should describe plans for the dissemination of the results for the project team as a whole and for individual participants. Details should include anticipated numbers of publications in refereed journals, articles in trade journals etc., presentations or demonstrations to the scientific community, trade organisations and internal reports or publications. Plans to make any information and/or reports available on the internet with the FSA's permission are also useful, however, this does not remove the requirement for Tenderers to think how best to target the output to relevant groups.

If a final report is part of the requirement, please make sure, as part of the executive summary, that aims and results are clear to the general audience and that the impact of the research on public health/consumers and it's alignment to FSA priorities is clearly stated.

Please note that permission to publish or to present findings from work supported by the FSA will be agreed in advance from the relevant FSA Project Officer. The Supplier will circulate proposed publications at least 30 days in advance of submission for publication. Each Party retains the right to request (such request not to be unreasonably refused) the delay of a publication in order to seek intellectual property protection for New IPR generated in the course of the Project if publication would reasonably prejudice such protection. Such delay shall not exceed 3 months, unless mutually agreed between the relevant Parties. Notification of the requirement for delay in submission for publication must be received by the publishing Supplier within thirty (30) days after the receipt of the proposed publication by the FSA and publishing Supplier will send a reminder noticed to FSA if it has received no acknowledgement from FSA regarding the proposed publication at least 10 days in advance of submission for publication, failing which the publishing Supplier shall be free to assume that FSA has no objection to the proposed publication.. The financial support of the FSA must also be acknowledged in publications.

Please indicate whether any Intellectual Property (IP) may be generated by this project and how this could be exploited. Please be aware the FSA retains all rights to the intellectual property generated along with all models developed during the life of the fellowship and where appropriate may exploit the IP generated for the benefit of public health.

In this part Applicants should demonstrate the credibility of the partnership for exploitation of the results and explain the partnership's policy in respect of securing patents or granting licenses for the technology (if applicable). It should deal with any possible agreements between the partners to extend their co-operation in the exploitation phase and with relevant agreements with companies, in particular users, external to the partnership.

Anticipated outputs include:

a) Published bespoke technical reports and/or peer-reviewed papers focussed on recommendations for enhancing risk assessment through the use of computational toxicology data and technologies. Any outputs published on the FSA websites should be made accessible in line with our public service commitment, refer to Accessibility Guidance

b) Established hub engaging FSA, SAC members and others with computational toxicology expertise in public bodies, industry and academia.

c) Dissemination of information through workshops within and wider than the FSA.

d) Potential longer-term relationship to maintain mutual knowledge exchange.

e) Ultimately, the established tool(s) needs to be of value beyond the life of the fellowship and aid in risk assessment long term. Before completion of the fellowship, members of the FSA will need to have been fully trained in the use of the developed tool(s). Any tools or models developed will remain the property of the FSA.

As academic scientists focused on translational research we are extremely aware of the need to disseminate - and receive feedback - on the results from our projects, and that is equally true for this Fellowship proposal.

We intend to exploit multiple methods of communication:

Project website – we will describe the project and partnership with the FSA on our UoB website [redacted]

Targeted press releases – for publication of news in national outlets, in particular to target consumers on topics such as reduction in animal use and product safety.

Conference and workshop activities – we believe the most relevant international meeting to present, receive feedback, and more broadly to learn of other international activities in non-animal chemical risk assessments, is for the Fellow to attend the annual Accelerating the Pace of Chemical Risk Assessment (APCRA) consortium (funding has been requested to attend all four APCRA meetings through the project). Indeed we also recommend that FSA scientists attend this annual event. We have proposed the Fellow presents at three of these four annual meetings.

Online communities – if allowed by FSA policy, we will encourage the Fellow to establish a Twitter account for the project, to help to continue building the community in computational toxicology. In addition, to write blogs for the same purpose.

Peer-reviewed publications – two publications, led by the Fellow and including the FSA/UoB/HSE Science and Research Centre, are defined as Deliverables for the project, the first focussed on challenges and opportunities for enhancing risk assessment through the use of computational toxicology, and the second describing Case Study 1 in order to provide a tangible example of the methods (funding has been requested for two open-access journal publications). We anticipate that the Fellow - and the wider project team - will contribute to further peer-reviewed publications, beyond the scope of the formal Deliverables.

Internal reports – two internal reports will be written, the first introducing NAMs and describing our recommendations for their implementation at the FSA, including proposed case studies. In addition to providing direction for the Fellow's applied research, we intend for this document to generate a broader and deeper understanding by the FSA (leadership) of the roles of computational NAMs in the safety assessment of regulated products - at the midpoint of the 4-yr project. The second report ('Final report') will describe the activities undertaken by the Fellow and the key outcomes of the 4-yr programme. We intend for this document, amongst other purposes, to assist the FSA in reporting back to the Government on the success of the programme.

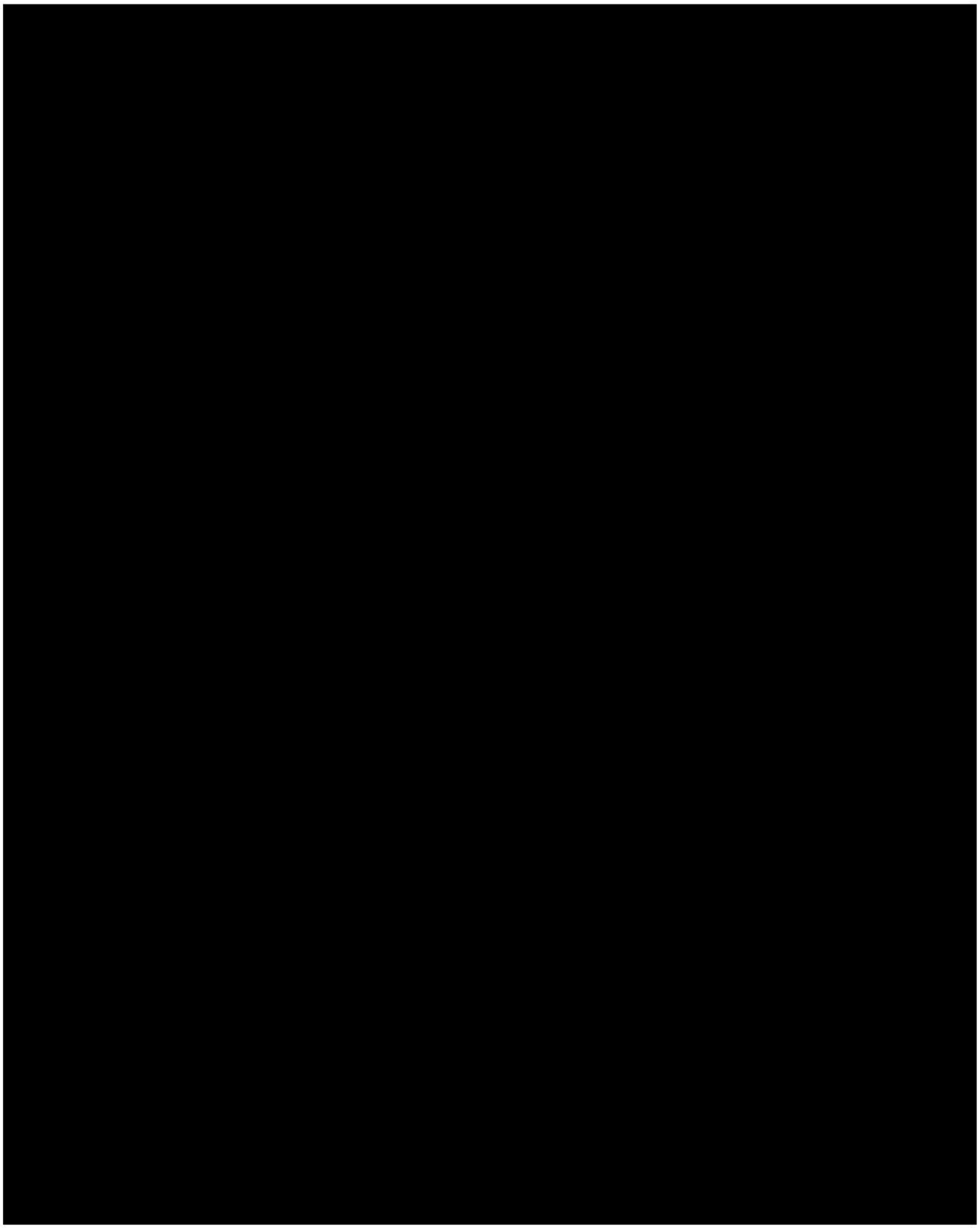
Industry engagement – we will seek to disseminate the findings from this partnership to industry, for example via a short article in the form of a business brief. Through our active (and current) collaborations with industry in the consumer products and agrichemicals sectors, we will request advice on publication outlets that they value the most.

Regulatory engagement – as an active member of the OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (and a co-Chair of the Omics Reporting Framework project, defining regulatory standards for reporting the generation and computational analysis of omics data), Viant will seek opportunities to disseminate progress from the proposed partnership. In addition, we will utilise our links to the European Food Safety Authority to disseminate findings; Dr Jean-Lou Dorne (Senior Scientific Officer in Toxicology, EFSA) has an Honorary academic appointment at the University of Birmingham.

We do not envision IP will be generated in this project for the reasons introduced in Section 2, specifically that the overarching need is to develop a common, transparent and reliable approach for biologically-based, quantitative, chemical safety assessments for chemicals. This is the very foundation from which global harmonisation of chemical safety assessments can be built, as widely recognised including by the International Programme on Chemical Safety and the Organisation for Economic Co-operation and Development. Indeed our research teams at UoB and the HSE Science and Research Centre highly value transparency of methods and open data (e.g., Viant serves on the Editorial Board for Nature Research's *Scientific Data* journal that promotes such qualities). We propose a Data Management Plan (DMP) could be prepared according to open access principles, to provide solutions and guidelines in all areas of data and model management, integration, use and dissemination, conforming to the FAIR Principle (Findable, Accessible, Interoperable and Reusable). The Fellow will be responsible for the data management and will also survey existing community-driven metadata standards (minimum information requirements, terminologies and formats) to identify other mature and suitable community practices, using FAIRsharing as well as the EISC Turning FAIR Data into Reality. FAIRsharing is an informative and educational resource of grass-roots and formal standards for the reporting, representation, access and sharing of data and metadata (*Nat. Biotechnol.* 2019; 37(4):358-367 doi: 10.1038/s41587-019-0080-8).

Annex 4 – Suppliers Financial Proposal

Organisation



The Food Standards Agency collaborates with our suppliers to improve efficiency and performance to save the taxpayer money. A tenderer should include in their tender the extent of any discounts or rebates offered against their normal day rates or other costs during each year of the contract. Please provide full details below:

Overheads and indirect rates for the Fellow position have been significantly reduced via match-funding provided by the University of Birmingham, leading to a discount of £[redacted] per year, equating to a total discount of £[redacted] across the course of the contract. In addition, [redacted] (HSE Science and Research Centre) is providing his time in-kind.

Staff Costs

[redacted]

[redacted]

Consumables/Equipment costs

Please add extra rows as required

[redacted]

Travel and Subsistence costs

Please add extra rows as required

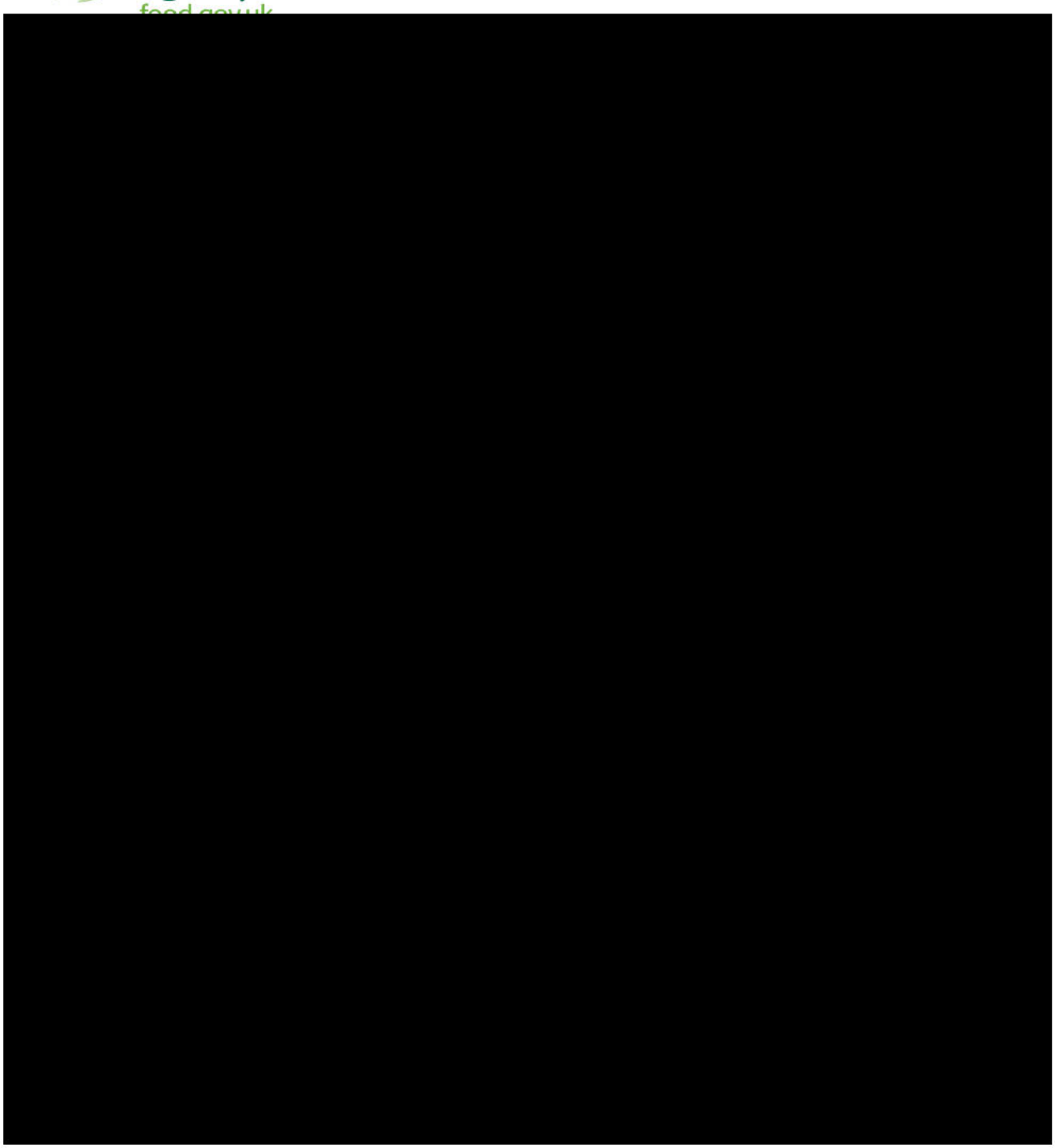
Purpose of journey or description of subsistence cost	Frequ-ency	Cost each (£)	Total Cost (£)

[redacted]

Other costs

Please add extra rows as required

Item (with purpose and justification)	Quantity	Cost/item	Total

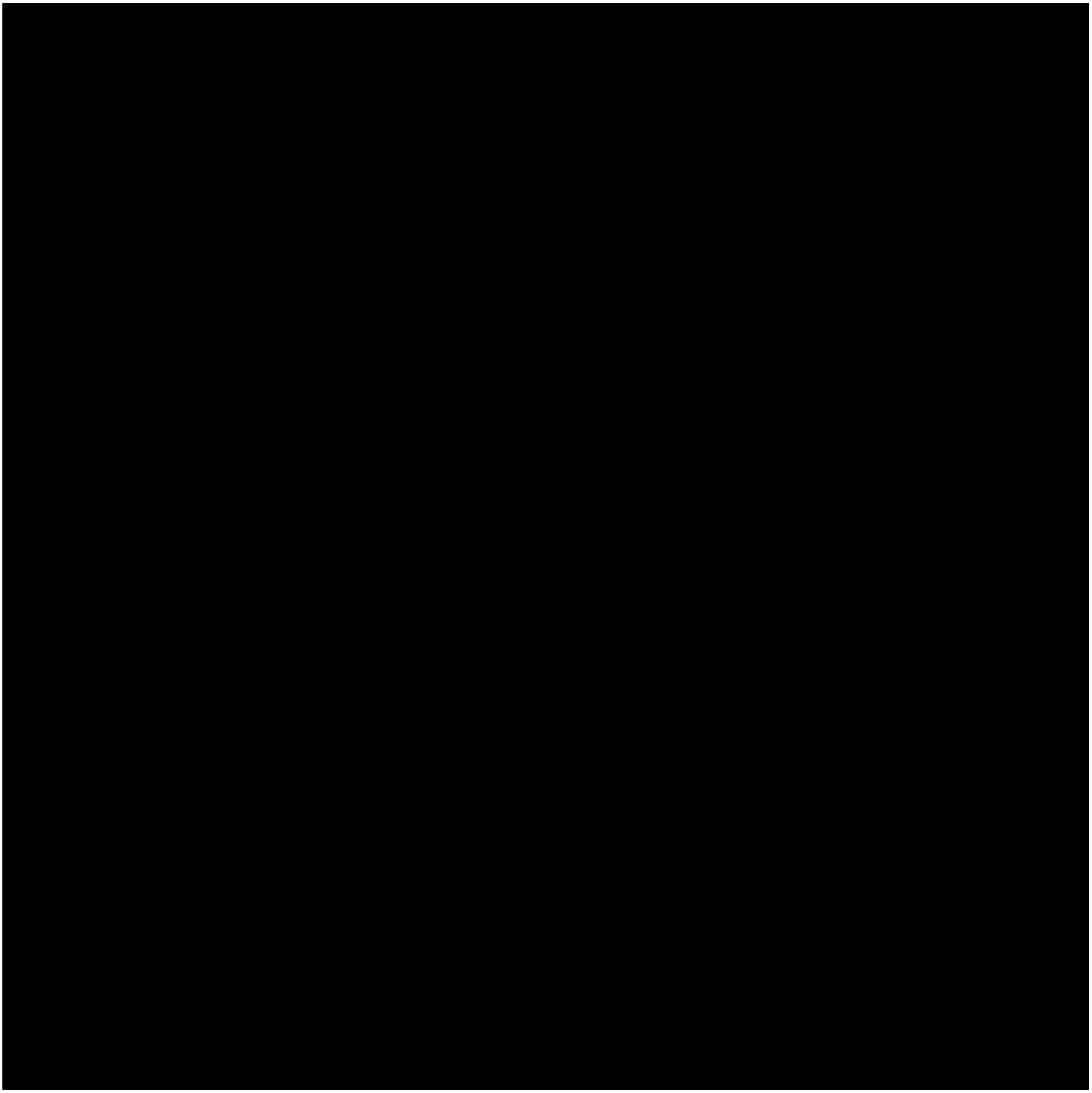


Schedule of payments

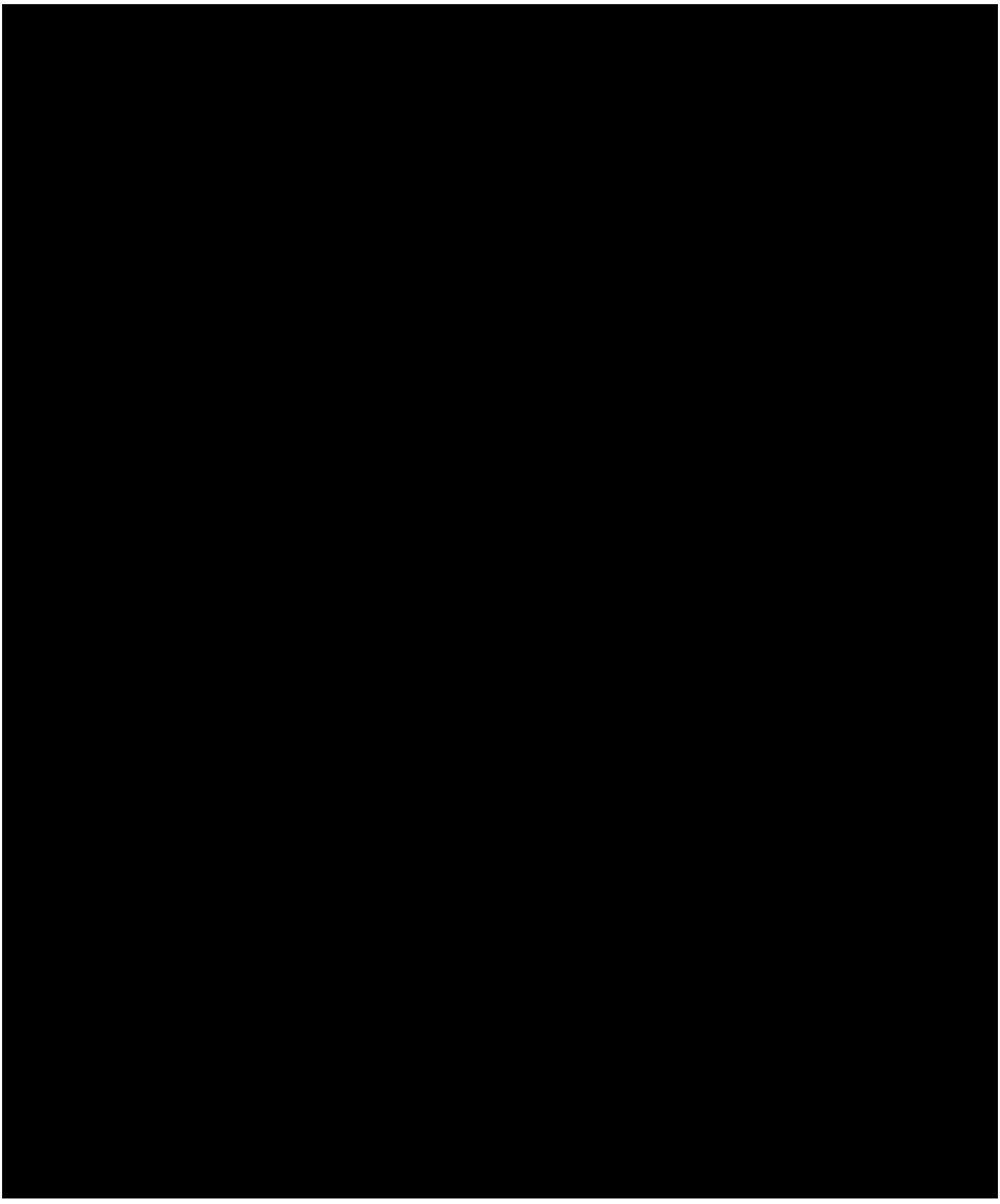
Please add extra rows as required

Proposed start date: **02 August 2021**

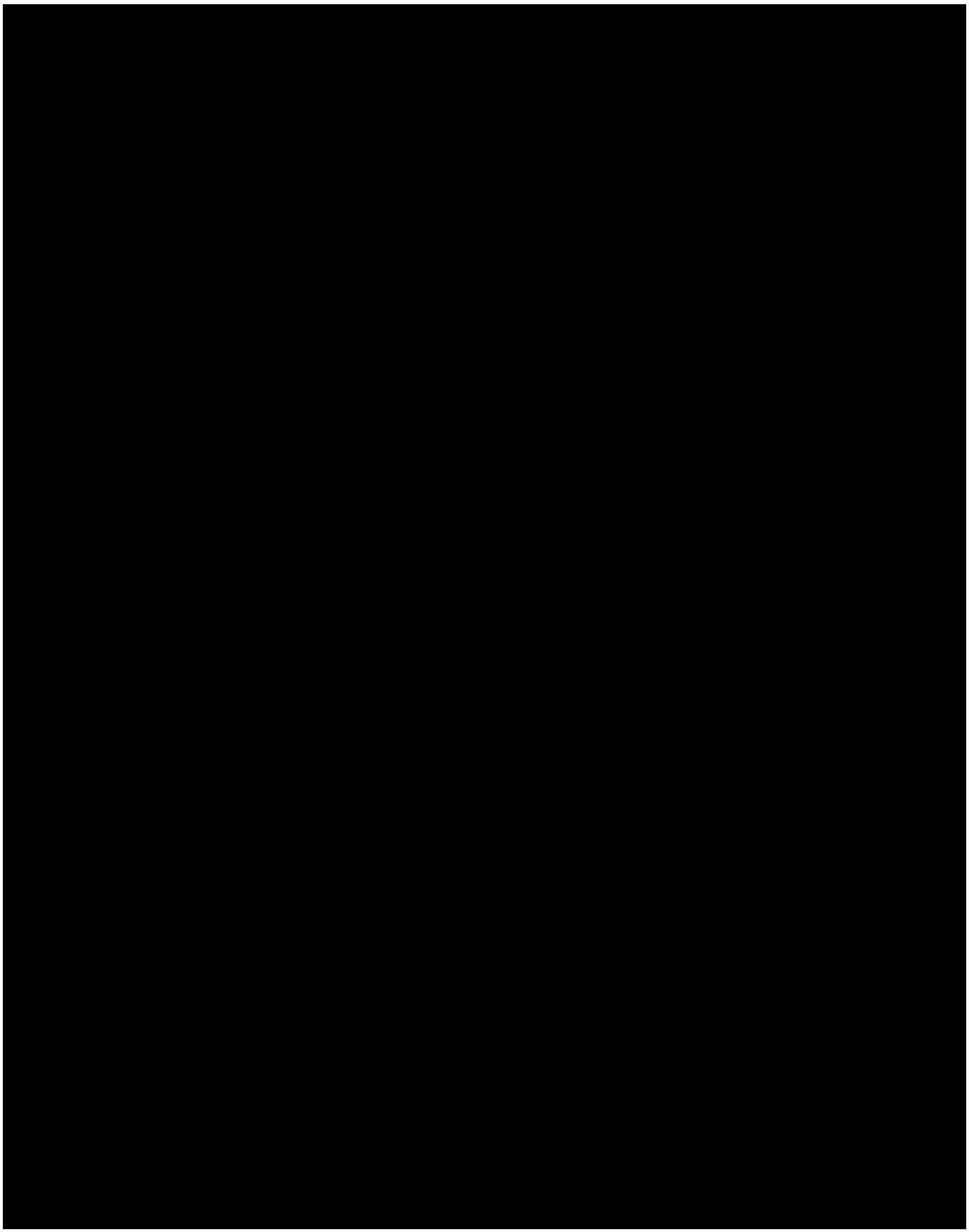
Year One Schedule



Year Two Schedule

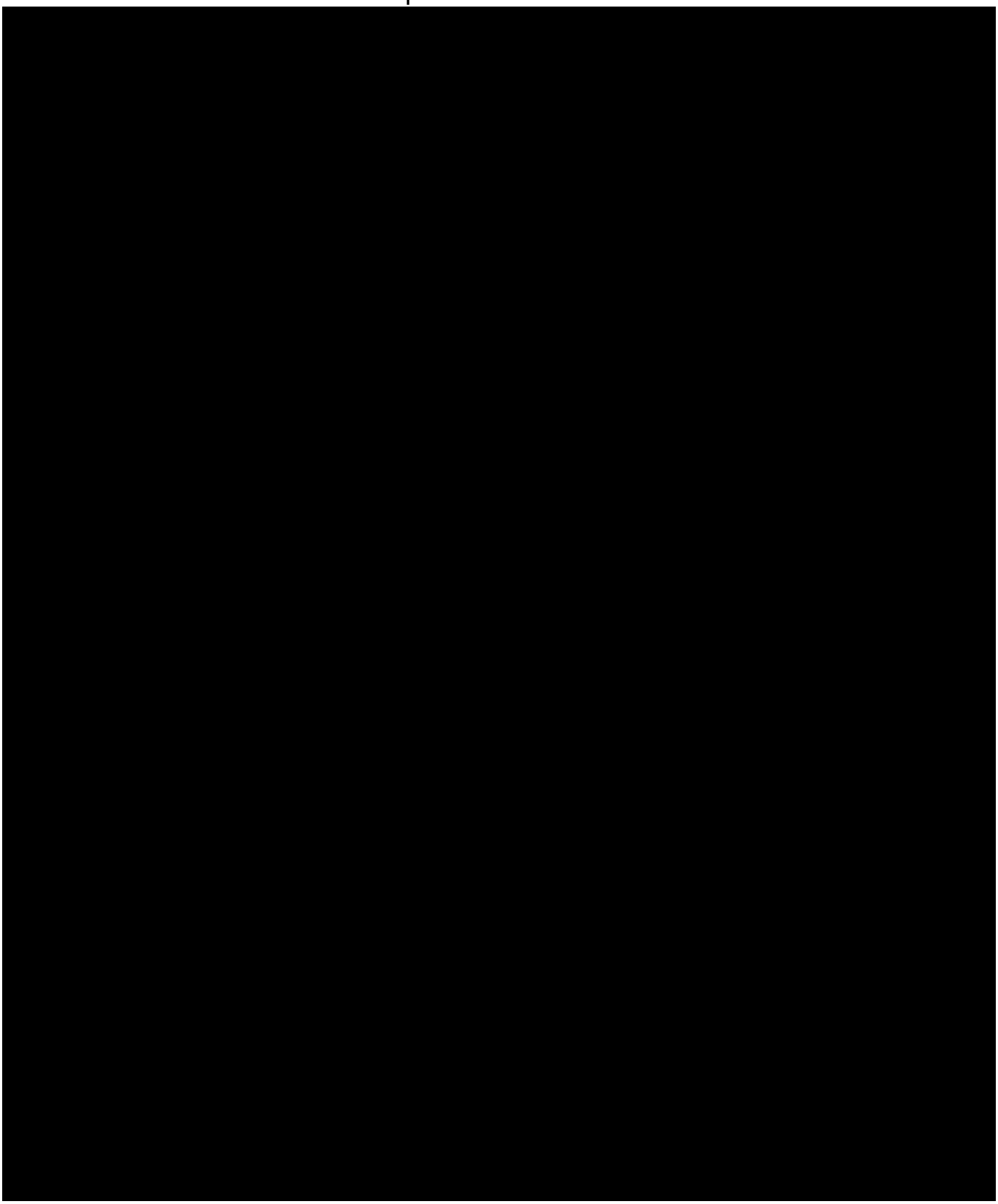


Year Three Schedule



Year Four Schedule

Please add extra rows as required



Short form Terms

1. Definitions used in the Contract

In this Contract, unless the context otherwise requires, the following words shall have the following meanings:

"Central Government Body"	means a body listed in one of the following sub-categories of the Central Government classification of the Public Sector Classification Guide, as published and amended from time to time by the Office for National Statistics: a) Government Department; b) Non-Departmental Public Body or Assembly Sponsored Public Body (advisory, executive, or tribunal); c) Non-Ministerial Department; or d) Executive Agency;
"Charges"	means the charges for the Deliverables as specified in the Order Form;
"Confidential Information"	means all information, whether written or oral (however recorded), provided by the disclosing Party to the receiving Party and which (i) is known by the receiving Party to be confidential; (ii) is marked as or stated to be confidential; or (iii) ought reasonably to be considered by the receiving Party to be confidential;
"Contract"	means the contract between (i) the Buyer and (ii) the Supplier which is created by the Supplier's counter signing the Order Form and includes the Order Form and Annexes;
"Controller"	has the meaning given to it in the GDPR;
"Buyer"	means the person identified in the letterhead of the Order Form;
"Date of Delivery"	means that date by which the Deliverables must be delivered to the Buyer, as specified in the Order Form;
"Buyer Cause"	any breach of the obligations of the Buyer or any other default, act, omission, negligence or statement of the Buyer, of its employees, servants, agents in connection with or in relation to the subject-matter of the Contract and in respect of which the Buyer is liable to the Supplier;
"Data Protection Legislation"	(i) the GDPR, the LED and any applicable national implementing Laws as amended from time to time (ii) the Data Protection Act 2018 to the extent that it relates to processing

	of personal data and privacy; (iii) all applicable Law about the processing of personal data and privacy;
"Data Protection Impact Assessment"	an assessment by the Controller of the impact of the envisaged processing on the protection of Personal Data;
"Data Protection Officer"	has the meaning given to it in the GDPR;
"Data Subject"	has the meaning given to it in the GDPR;
"Data Loss Event"	any event that results, or may result, in unauthorised access to Personal Data held by the Supplier under this Contract, and/or actual or potential loss and/or destruction of Personal Data in breach of this Contract, including any Personal Data Breach;
"Data Subject Access Request"	a request made by, or on behalf of, a Data Subject in accordance with rights granted pursuant to the Data Protection Legislation to access their Personal Data;
"Deliver"	means hand over the Deliverables to the Buyer at the address and on the date specified in the Order Form. Delivered and Delivery shall be construed accordingly;
"Existing IPR"	any and all intellectual property rights that are owned by or licensed to either Party and which have been developed independently of the Contract (whether prior to the date of the Contract or otherwise);
"Expiry Date"	means the date for expiry of the Contract as set out in the Order Form;
"FOIA"	means the Freedom of Information Act 2000 together with any guidance and/or codes of practice issued by the Information Commissioner or relevant Government department in relation to such legislation;
"Force Majeure Event"	any event, occurrence, circumstance, matter or cause affecting the performance by either Party of its obligations under the Contract arising from acts, events, omissions, happenings or non-happenings beyond its reasonable control which prevent or materially delay it from performing its obligations under the Contract but excluding: i) any industrial dispute relating to the Supplier, the Supplier Staff (including any subsets of them) or any other failure in the Supplier or the Subcontractor's supply chain; ii) any event, occurrence, circumstance, matter or cause which is attributable to the wilful act, neglect or failure to take reasonable precautions against it by the Party concerned; and iii) any failure of delay caused by a lack of funds;

"GDPR"	the General Data Protection Regulation (Regulation (EU) 2016/679);
"Goods"	means the goods to be supplied by the Supplier to the Buyer under the Contract;
"Good Industry Practice"	standards, practices, methods and procedures conforming to the law and the exercise of the degree of skill and care, diligence, prudence and foresight which would reasonably and ordinarily be expected from a skilled and experienced person or body engaged within the relevant industry or business sector;
"Government Data"	a) the data, text, drawings, diagrams, images or sounds (together with any database made up of any of these) which are embodied in any electronic, magnetic, optical or tangible media, including any of the Buyer's confidential information, and which: i) are supplied to the Supplier by or on behalf of the Buyer; or ii) the Supplier is required to generate, process, store or transmit pursuant to the Contract; or b) any Personal Data for which the Buyer is the Data Controller;
"Information"	has the meaning given under section 84 of the FOIA;
"Information Commissioner"	the UK's independent authority which deals with ensuring information relating to rights in the public interest and data privacy for individuals is met, whilst promoting openness by public bodies;
"Insolvency Event"	in respect of a person: a) if that person is insolvent; ii) if an order is made or a resolution is passed for the winding up of the person (other than voluntarily for the purpose of solvent amalgamation or reconstruction); iii) if an administrator or administrative receiver is appointed in respect of the whole or any part of the persons assets or business; iv) if the person makes any composition with its creditors or takes or suffers any similar or analogous action to any of the actions detailed in this definition as a result of debt in any jurisdiction;
"Intellectual Property Rights (IPRs)"	means patents, inventions, registered designs, copyrights, database rights, domain names, design rights, copyright, rights affording equivalent protection to copyright, database rights, design rights, topography rights, trade marks, service marks, business names, trade names, moral rights, registration of or an application to register any of the aforesaid items, and rights in the nature of any of the aforesaid items in any country, rights in the nature of unfair competition rights and rights to sue for passing off.
"Key Personnel"	means any persons specified as such in the Order Form or otherwise notified as such by the Buyer to the Supplier in writing;
"LED"	Law Enforcement Directive (Directive (EU) 2016/680);

"New IPR"	all IPR in any materials created or developed by or on behalf of the Supplier pursuant to the Contract but shall not include the Supplier's Existing IPR or in the Training Course(s) Material;
"Order Form"	means the letter from the Buyer to the Supplier printed above these terms and conditions;
"Party"	the Supplier or the Buyer (as appropriate) and "Parties" shall mean both of them;
"Personal Data"	has the meaning given to it in the GDPR;
"Training Course(s) Materials"	mean the information, documents and presentations created by the Supplier for the Training Course(s) as detailed in the Project Plan and Deliverables during the Term

"Purchase Order Number"	means the Buyer's unique number relating to the order for Deliverables to be supplied by the Supplier to the Buyer in accordance with the terms of the Contract;
"Regulations"	the Public Contracts Regulations 2015 and/or the Public Contracts (Scotland) Regulations 2015 (as the context requires) as amended from time to time;
"Request for Information"	has the meaning set out in the FOIA or the Environmental Information Regulations 2004 as relevant (where the meaning set out for the term "request" shall apply);
"Services"	means the services to be supplied by the Supplier to the Buyer under the Contract;
"Specification"	means the specification for the Deliverables to be supplied by the Supplier to the Buyer (including as to quantity, description and quality) as specified in the Order Form;
"Staff"	means all directors, officers, employees, agents, consultants and contractors of the Supplier and/or of any sub-contractor of the Supplier engaged in the performance of the Supplier's obligations under the Contract;
"Staff Vetting Procedures"	means vetting procedures that accord with good industry practice or, where applicable, the Buyer's procedures for the vetting of personnel as provided to the Supplier from time to time;
"Supplier Staff"	all directors, officers, employees, agents, consultants and contractors of the Supplier and/or of any Subcontractor engaged in the performance of the Supplier's obligations under a Contract;
"Supplier"	means the person named as Supplier in the Order Form;
"Term"	means the period from the start date of the Contract set out in the Order Form to the Expiry Date as such period may be extended in accordance with clause [ ] or terminated in accordance with the terms and conditions of the Contract;

"VAT"	means value added tax in accordance with the provisions of the Value Added Tax Act 1994;
"Workers"	any one of the Supplier Staff which the Buyer, in its reasonable opinion, considers is an individual to which Procurement Policy Note 08/15 (Tax Arrangements of Public Appointees) (https://www.gov.uk/government/publications/procurement-policynote-0815-tax-arrangements-of-appointees) applies in respect of the Deliverables;
"Working Day"	means a day (other than a Saturday or Sunday) on which banks are open for business in the City of London.

2. Understanding the Contract

In the Contract, unless the context otherwise requires:

2.1 references to numbered clauses are references to the relevant clause in these terms and conditions;

2.2 any obligation on any Party not to do or omit to do anything shall include an obligation not to allow that thing to be done or omitted to be done;

2.3 the headings in this Contract are for information only and do not affect the interpretation of the Contract;

2.4 references to "writing" include printing, display on a screen and electronic transmission and other modes of representing or reproducing words in a visible form;

2.5 the singular includes the plural and vice versa;

2.6 a reference to any law includes a reference to that law as amended, extended, consolidated or re-enacted from time to time and to any legislation or byelaw made under that law; and

2.7 the word ‘including’, "for example" and similar words shall be understood as if they were immediately followed by the words "without limitation".

3. How the Contract works

3.1 The Order Form is an offer by the Buyer to purchase the Deliverables subject to and in accordance with the terms and conditions of the Contract.

3.2 The Supplier is deemed to accept the offer in the Order Form when the Buyer receives a copy of the Order Form signed by the Supplier.

4. What needs to be delivered

4.1 All Deliverables

(a) The Supplier must provide Deliverables: (i) in accordance with the Specification; (ii) to a professional standard; (iii) using reasonable skill and care; (iv) using Good Industry Practice; (v) using its own policies, processes and internal quality control measures as long as they don't conflict with the Contract; (vi) on the dates agreed; and (vii) that comply with all law.

4.2 Goods clauses- Not Used

4.3 Services clauses

(a) Late delivery of the Services will be a default of the Contract.

(b) The Supplier must co-operate with the Buyer and third party suppliers on all aspects connected with the delivery of the Services and ensure that Supplier Staff comply with any reasonable instructions including any security requirements.

(c) The Buyer must provide the Supplier with reasonable access to its premises at reasonable times for the purpose of supplying the Services

(d) The Supplier must at its own risk and expense provide all equipment required to deliver the Services. Any equipment provided by the Buyer to the Supplier for supplying the Services remains the property of the Buyer and is to be returned to the Buyer on expiry or termination of the Contract.

(e) The Supplier must allocate sufficient resources and appropriate expertise to the Contract.

(f) The Supplier must take all reasonable care to ensure performance does not disrupt the Buyer's operations, employees or other contractors.

(g) On completion of the Services, the Supplier is responsible for leaving the Buyer's premises in a clean, safe and tidy condition and making good any damage that it has caused to the Buyer's premises or property, other than fair wear and tear.

(h) The Supplier must ensure all Services, and anything used to deliver the Services, are of good quality.

(i) The Buyer is entitled to withhold payment for partially or undelivered Services, but doing so does not stop it from using its other rights under the Contract.

5. Pricing and payments

5.1 In exchange for the Deliverables, the Supplier shall be entitled to invoice the Buyer for the charges in the Order Form. The Supplier shall raise invoices promptly and in any event within 90 days from when the charges are due.

5.2 All Charges:

(a) exclude VAT, which is payable on provision of a valid VAT invoice;

(b) include all costs connected with the supply of Deliverables.

5.3 The Buyer must pay the Supplier the charges within 30 days of receipt by the Buyer of a valid, undisputed invoice, in cleared funds to the Supplier's account stated in the Order Form.

5.4 A Supplier invoice is only valid if it:

(a) includes all appropriate references including the Purchase Order Number and other details reasonably requested by the Buyer;

(b) includes a detailed breakdown of Deliverables which have been delivered (if any).

5.5 If there is a dispute between the Parties as to the amount invoiced, the Buyer shall pay the undisputed amount whilst the Parties seek to resolve the dispute as detailed under clause 33. The Supplier shall not suspend the provision of the Deliverables unless the Supplier is entitled to terminate the Contract for a failure to pay undisputed sums in accordance with clause 11.6. Any disputed amounts shall be resolved through the dispute resolution procedure detailed in clause 33.

5.6 The Buyer may retain or set-off payment of any amount owed to it by the Supplier if notice and reasons are provided.

5.7 The Supplier must ensure that all subcontractors are paid, in full, within 30 days of receipt of a valid, undisputed invoice. If this doesn't happen, the Buyer can publish the details of the late payment or non-payment.

6. The Buyer's obligations to the Supplier

6.1 If Supplier fails to comply with the Contract as a result of a Buyer Cause:

(a) the Buyer cannot terminate the Contract under clause 11;
(b) the Supplier is entitled to reasonable and proven additional expenses and to relief from liability under this Contract;
(c) the Supplier is entitled to additional time needed to deliver the Deliverables;
(d) the Supplier cannot suspend the ongoing supply of Deliverables.

6.2 Clause 6.1 only applies if the Supplier:

(a) gives notice to the Buyer within 10 Working Days of becoming aware;
(b) demonstrates that the failure only happened because of the Buyer Cause;
(c) mitigated the impact of the Buyer Cause.

7. Record keeping and reporting

7.1 The Supplier must ensure that suitably qualified representatives attend progress meetings with the Buyer and provide progress reports when specified in the Order Form.

7.2 The Supplier must keep and maintain full and accurate records and accounts on everything to do with the Contract for seven years after the date of expiry or termination of the Contract.

7.3 The Supplier must allow any auditor appointed by the Buyer access to their premises to verify all contract accounts and records of everything to do with the Contract and provide copies for the audit. The Supplier shall ensure that any third party auditor appointed by the Buyer are bound by terms of confidentiality at least as restrictive as those in this Agreement prior to being given access to the Suppliers premises, contract accounts and records.

7.4 The Supplier must provide information to the auditor and reasonable co-operation at their request.

7.5 If the Supplier is not providing any of the Deliverables, or is unable to provide them, it must immediately:

(a) tell the Buyer and give reasons;
(b) propose corrective action;
(c) provide a deadline for completing the corrective action.

7.6 If the Buyer, acting reasonably, is concerned as to the financial stability of the Supplier such that it may impact on the continued performance of the Contract then the Buyer may:

(a) require that the Supplier provide to the Buyer (for its approval) a plan setting out how the Supplier will ensure continued performance of the Contract and the Supplier will make changes to such plan as reasonably required by the Buyer and once it is agreed then the Supplier shall act in accordance with such plan and report to the Buyer on demand

(b) if the Supplier fails to provide a plan or fails to agree any changes which are requested by the Buyer or fails to implement or provide updates on progress with the plan, terminate the Contract immediately for material breach (or on such date as the Buyer notifies).

8. Supplier staff

8.1 The Supplier Staff involved in the performance of the Contract must:

(a) be appropriately trained and qualified;

(b) be vetted using Good Industry Practice.

(c) comply with all conduct requirements when on the Buyer's premises.

8.2 Where a Buyer decides one of the Supplier's Staff isn't suitable to work on the Contract, the Supplier must replace them with a suitably qualified alternative.

8.3 If requested, the Supplier must replace any person whose acts or omissions have caused the Supplier to breach clause 8.

8.4 The Supplier must provide a list of Supplier Staff needing to access the Buyer's premises and say why access is required.

8.5 The Supplier indemnifies the Buyer against all claims brought by any person employed by the Supplier caused by an act or omission of the Supplier or any Supplier Staff.

8.6 The Supplier shall use those persons nominated in the Order Form (if any) to provide the Deliverables and shall not remove or replace any of them unless:

(a) requested to do so by the Buyer (not to be unreasonably withheld or delayed);

(b) the person concerned resigns, retires or dies or is on maternity or long-term sick leave; or

(c) the person's employment or contractual arrangement with the Supplier or any subcontractor is terminated for material breach of contract by the employee.

9. Rights and protection

9.1 The Supplier warrants and represents that:

(a) it has full capacity and authority to enter into and to perform the Contract;

(b) the Contract is executed by its authorised representative;

(c) it is a legally valid and existing organisation incorporated in the place it was formed;

(d) there are no known legal or regulatory actions or investigations before any court, administrative body or arbitration tribunal pending or threatened against it that might affect its ability to perform the Contract;
(e) it maintains all necessary rights, authorisations, licences and consents to perform its obligations under the Contract;
(f) it doesn't have any contractual obligations which are likely to have a material adverse effect on its ability to perform the Contract; and
(g) it is not impacted by an Insolvency Event.

9.2 The warranties and representations in clause 9.1 are repeated each time the Supplier provides Deliverables under the Contract.

9.3 The Supplier indemnifies the Buyer against each of the following:
(a) wilful misconduct of the Supplier, any of its subcontractor and/or Supplier Staff that impacts the Contract;
(b) non-payment by the Supplier of any tax or National Insurance.

9.4 If the Supplier becomes aware of a representation or warranty that becomes untrue or misleading, it must immediately notify the Buyer.

9.5 All third party warranties and indemnities covering the Deliverables must be assigned for the Buyer's benefit by the Supplier.

10. Intellectual Property Rights (IPRs)

10.1 Each Party keeps ownership of its own Existing IPRs. The Supplier gives the Buyer a non-exclusive, perpetual, royalty-free, irrevocable, transferable worldwide license to use, and sub-license the Supplier's Existing IPR to enable it and its sub- licensees to both:
(a) receive and use the Deliverables;
(b) use the New IPR (non-commercial use only).

10.2 Any New IPR created under the Contract is owned by the Buyer. The Buyer gives the Supplier a non-exclusive, perpetual, royalty-free, irrevocable, transferable worldwide license to use and sublicense any of the Buyer's Existing IPRs for the purpose of fulfilling its obligations under the Contract and in order to exercise rights under the New IPR. The Buyer gives the Supplier a perpetual, royalty-free, non-exclusive, license to use and sub license any New IPRs for teaching and research purposes. For the avoidance of doubt, this license includes the right for the Supplier to use and sub license the Training Course Materials for commercial teaching and training which may be provided by the Supplier, the Supplier's affiliate University of Birmingham Enterprise Ltd and by the Supplier's sub-contractor Michabo Health Science Ltd.

10.3 Where a Party acquires ownership of intellectual property rights incorrectly under this Contract it must do everything reasonably necessary to complete a transfer assigning them in writing to the other Party on request and at its own cost.

10.4 Neither Party has the right to use the other Party's intellectual property rights, including any use of the other Party's names, logos or trademarks, except as provided in clause 10 or otherwise agreed in writing.

10.5 If any claim is made against the Buyer for actual or alleged infringement of a third party's intellectual property arising out of, or in connection with, the supply or use of the Deliverables ("**IPR Claim**"), then the Supplier indemnifies the Buyer against all

losses, damages, costs or expenses (including professional fees and fines) incurred as a result of the IPR Claim.

10.6 If an IPR Claim is made or anticipated the Supplier must at its own expense and the Buyer's sole option, either:

(a) obtain for the Buyer the rights in clauses 10.1 and 10.2 without infringing any third party intellectual property rights;

(b) replace or modify the relevant item with substitutes that don't infringe intellectual property rights without adversely affecting the functionality or performance of the Deliverables.

11. Ending the contract

11.1 The Contract takes effect on the commencement date specified in the Order Form and ends on the earlier of the date of expiry specified in the Order Form or termination of the Contract.

11.2 The Buyer can extend the Contract where set out in the Order Form in accordance with the terms in the Order Form.

11.3 Ending the Contract without a reason

The Buyer has the right to terminate the Contract at any time without reason or liability by giving the Supplier not less than 90 days' written notice and if it's terminated clause 11.5(b) to 11.5(g) applies.

11.4 When the Buyer can end the Contract

(a) If any of the following events happen, the Buyer has the right to immediately terminate its Contract by issuing a termination notice in writing to the Supplier:

(i) there's a Supplier Insolvency Event;

(ii) if the Supplier repeatedly breaches the Contract in a way to reasonably justify the opinion that its conduct is inconsistent with it having the intention or ability to give effect to the terms and conditions of the Contract;

(iii) if the Supplier is in material breach of any obligation which is capable of remedy, and that breach is not remedied within 30 days of the Supplier receiving notice specifying the breach and requiring it to be remedied;

(iv) there's a change of control (within the meaning of section 450 of the Corporation Tax Act 2010) of the Supplier which isn't pre-approved by the Buyer in writing;

(v) if the Buyer discovers that the Supplier was in one of the situations in 57 (1) or 57(2) of the Regulations at the time the Contract was awarded;

(vi) the Court of Justice of the European Union uses Article 258 of the Treaty on the Functioning of the European Union (TFEU) to declare that the Contract should not have been awarded to the Supplier because of a serious breach of the TFEU or the Regulations;

(vii) the Supplier embarrass or bring the Buyer into disrepute or diminish the public trust in them.

(b) If any of the events in 73(1) (a) to (c) of the Regulations (substantial modification, exclusion of the Supplier, procurement infringement) happen, the Buyer has the right to immediately terminate the Contract and clause 11.5(b) to 11.5(g) applies.

11.5 What happens if the Contract ends

Where the Buyer terminates the Contract under clause 11.4(a) all of the following apply:

(a) the Buyer's payment obligations under the terminated Contract stop immediately;

(b) accumulated rights of the Parties are not affected;

(c) the Supplier must promptly delete or return the Government Data except where required to retain copies by law;

(d) the Supplier must promptly return any of the Buyer's property provided under the Contract;

(e) the Supplier must, at no cost to the Buyer, give all reasonable assistance to the Buyer and any incoming supplier and co-operate fully in the handover and re-procurement;

(f) the following clauses survive the termination of the Contract: [3.2.10, 6, 7.2, 9, 11, 14, 15, 16, 17, 18, 34, 35] and any clauses which are expressly or by implication intended to continue.

11.6 When the Supplier can end the Contract

(a) The Supplier can issue a reminder notice if the Buyer does not pay an undisputed invoice on time. The Supplier can terminate the Contract if the Buyer fails to pay an undisputed invoiced sum due and worth over 10% of the total Contract value or £1,000, whichever is the lower, within 30 days of the date of the reminder notice.

(b) If a Supplier terminates the Contract under clause 11.6(a):

(i) the Buyer must promptly pay all outstanding charges incurred to the Supplier;

(ii) the Buyer must pay the Supplier reasonable committed and unavoidable losses as long as the Supplier provides a fully itemised and costed schedule with evidence - the maximum value of this payment is limited to the total sum payable to the Supplier if the Contract had not been terminated;

(iii) clauses 11.5(d) to 11.5(g) apply.

11.7 Partially ending and suspending the Contract

(a) Where the Buyer has the right to terminate the Contract it can terminate or suspend (for any period), all or part of it. If the Buyer suspends the Contract it can provide the Deliverables itself or buy them from a third party.

(b) The Buyer can only partially terminate or suspend the Contract if the remaining parts of it can still be used to effectively deliver the intended purpose.

(c) The Parties must agree (in accordance with clause 24) any necessary variation required by clause 11.7.

(d) The Buyer can still use other rights available, or subsequently available to it if it acts on its rights under clause 11.7.

12. How much you can be held responsible for

12.1 Each Party's total aggregate liability under or in connection with the Contract (whether in tort, contract or otherwise) is no more than 125% of the Charges paid or payable to the Supplier.

12.2 No Party is liable to the other for:

(a) any indirect losses;

(b) loss of profits, turnover, savings, business opportunities or damage to goodwill (in each case whether direct or indirect).

12.3 In spite of clause 12.1, neither Party limits or excludes any of the following:

(a) its liability for death or personal injury caused by its negligence, or that of its employees, agents or subcontractors;

(b) its liability for bribery or fraud or fraudulent misrepresentation by it or its employees;

(c) any liability that cannot be excluded or limited by law.

12.4 In spite of clause 12.1, the Supplier does not limit or exclude its liability for any indemnity given under clauses 4.2(j), 4.2(m), 8.5, 9.3, 10.5, 13.2, 14.26(e) or 30.2(b).

12.5 Each Party must use all reasonable endeavours to mitigate any loss or damage which it suffers under or in connection with the Contract, including any indemnities.

12.6 If more than one Supplier is party to the Contract, each Supplier Party is fully responsible for both their own liabilities and the liabilities of the other Suppliers.

13. Obeying the law

13.1 The Supplier must, in connection with provision of the Deliverables, use reasonable endeavours to:

(a) comply and procure that its subcontractors comply with the Supplier Code of Conduct appearing at (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/779660/20190220-Supplier_Code_of_Conduct.pdf) and such other corporate social responsibility requirements as the Buyer may notify to the Supplier from time to time;

(b) support the Buyer in fulfilling its Public Sector Equality duty under S149 of the Equality Act 2010;

(c) not use nor allow its subcontractors to use modern slavery, child labour or inhumane treatment;

(d) meet the applicable Government Buying Standards applicable to Deliverables which can be found online at: https://www.gov.uk/government/collections/sustainable-procurement-the-government-buying-standards-gbs

13.2 The Supplier indemnifies the Buyer against any costs resulting from any default by the Supplier relating to any applicable law to do with the Contract.

13.3 The Supplier must appoint a Compliance Officer who must be responsible for ensuring that the Supplier complies with Law, Clause 13.1 and Clauses 27 to 32

13.4 "Compliance Officer" the person(s) appointed by the Supplier who is responsible for ensuring that the Supplier complies with its legal obligations;

14. Data protection

14.1 The Parties acknowledge and agree that as at the Effective Date any research data to be transferred pursuant to this Contract does not constitute Personal Data;

14.1.2 The Parties each acknowledge and agree that they may need to process Personal Data relating to each Party's representatives (in their respective capacities as data controllers) where relevant in order to:

14.1.2.1 administer and perform their respective activities and obligations under this Contract ; and

14.1.2.2 compile, dispatch and manage any payments agreed under this Contract; and

14.1.2.3 manage this Contract and resolve any disputes relating to it; and

14.1.2.4 respond and/or raise general queries relating to this Contract ; and

14.1.2.5 comply with their respective regulatory obligations; and

14.1.3 each Party shall process such Personal Data relating to each Party's representatives for the purposes set out in this clause in accordance with their respective privacy policies. The Parties acknowledge that they may be required to share Personal Data with other relevant parties, within or outside of the country of origin, in order to carry out the activities listed in this clause, and in doing so each Party will ensure that the sharing and use of this Personal Data complies with applicable data protection laws.

14.1.4 Although not contemplated under this Contract, if during the term of this Contract it becomes necessary to transfer any research data which contains any Personal Data, the Parties shall prior to any such transfer enter into a variation to the Contract to agree data transfer terms and to complete the template in Annex 1 of the Order Form (Authorised Processing) in such format as shall comply with applicable Data Protection Legislation.

15. What you must keep confidential

15.1 Each Party must:

(a) keep all Confidential Information it receives confidential and secure;

(b) not disclose, use or exploit the disclosing Party's Confidential Information without the disclosing Party's prior written consent, except for the purposes anticipated under the Contract;

(c) immediately notify the disclosing Party if it suspects unauthorised access, copying, use or disclosure of the Confidential Information.

15.2 In spite of clause 15.1, a Party may disclose Confidential Information which it receives from the disclosing Party in any of the following instances:

(a) where disclosure is required by applicable Law or by a court with the relevant jurisdiction if the recipient Party notifies the disclosing Party of the full circumstances, the affected Confidential Information and extent of the disclosure;

(b) if the recipient Party already had the information without obligation of

confidentiality before it was disclosed by the disclosing Party;

(c) if the information was given to it by a third party without obligation of confidentiality;

(d) if the information was in the public domain at the time of the disclosure;

(e) if the information was independently developed without access to the disclosing Party's Confidential Information;

(f) to its auditors or for the purposes of regulatory requirements;

(g) on a confidential basis, to its professional advisers on a need-to-know basis;

(h) to the Serious Fraud Office where the recipient Party has reasonable grounds to believe that the disclosing Party is involved in activity that may be a criminal offence under the Bribery Act 2010.

15.3 The Supplier may disclose Confidential Information on a confidential basis to Supplier Staff on a need-to-know basis to allow the Supplier to meet its obligations under the Contract. The Supplier Staff must enter into a direct confidentiality agreement with the Buyer at its request.

15.4 The Buyer may disclose Confidential Information in any of the following cases:

(a) on a confidential basis to the employees, agents, consultants and contractors of the Buyer;

(b) on a confidential basis to any other Central Government Body, any successor body to a Central Government Body or any company that the Buyer transfers or proposes to transfer all or any part of its business to;

(c) if the Buyer (acting reasonably) considers disclosure necessary or appropriate to carry out its public functions;

(d) where requested by Parliament;
(e) under clauses 5.7 and 16.

15.5 For the purposes of clauses 15.2 to 15.4 references to disclosure on a confidential basis means disclosure under a confidentiality agreement or arrangement including terms as strict as those required in clause 15.

15.6 Information which is exempt from disclosure by clause 16 is not Confidential Information.

15.7 The Supplier must not make any press announcement or publicise the Contract or any part of it in any way, without the prior written consent of the Buyer and must take all reasonable steps to ensure that Supplier Staff do not either.

16. When you can share information

16.1 The Supplier must tell the Buyer within ten (10) days if it receives a Request For Information.

16.2 Within the required timescales the Supplier must give the Buyer full co-operation and information needed so the Buyer can:
(a) comply with any Freedom of Information Act (FOIA) request;
(b) comply with any Environmental Information Regulations (EIR) request.

16.3 The Buyer may talk to the Supplier to help it decide whether to publish information under clause 16. However, the extent, content and format of the disclosure is the Buyer's decision, which does not need to be reasonable.

17. Invalid parts of the contract

If any part of the Contract is prohibited by Law or judged by a court to be unlawful, void or unenforceable, it must be read as if it was removed from that Contract as much as required and rendered ineffective as far as possible without affecting the rest of the Contract, whether it's valid or enforceable.

18. No other terms apply

The provisions incorporated into the Contract are the entire agreement between the Parties. The Contract replaces all previous statements and agreements whether written or oral. No other provisions apply.

19. Other people's rights in a contract

No third parties may use the Contracts (Rights of Third Parties) Act (CRTPA) to enforce any term of the Contract unless stated (referring to CRTPA) in the Contract. This does not affect third party rights and remedies that exist independently from CRTPA.

20. Circumstances beyond your control

20.1 Any Party affected by a Force Majeure Event is excused from performing its obligations under the Contract while the inability to perform continues, if it both:

(a) provides written notice to the other Party;
(b) uses all reasonable measures practical to reduce the impact of the Force Majeure Event.

20.2 Either party can partially or fully terminate the Contract if the provision of the Deliverables is materially affected by a Force Majeure Event which lasts for 90 days continuously.

20.3 Where a Party terminates under clause 20.2:
(a) each party must cover its own losses;
(b) clause 11.5(a) to 11.5(g) applies.

21. Relationships created by the contract

The Contract does not create a partnership, joint venture or employment relationship. The Supplier must represent themselves accordingly and ensure others do so.

22. Giving up contract rights

A partial or full waiver or relaxation of the terms of the Contract is only valid if it is stated to be a waiver in writing to the other Party.

23. Transferring responsibilities

23.1 The Supplier cannot assign the Contract without the Buyer's written consent.

23.2 The Buyer can assign, novate or transfer its Contract or any part of it to any Crown Body, public or private sector body which performs the functions of the Buyer.

23.3 When the Buyer uses its rights under clause 23.2 the Supplier must enter into a novation agreement in the form that the Buyer specifies.

23.4 The Supplier can terminate the Contract novated under clause 23.2 .

23.5 The Supplier remains responsible for all acts and omissions of the Supplier Staff as if they were its own.

23.6 If the Buyer asks the Supplier for details about Subcontractors, the Supplier must provide details of Subcontractors at all levels of the supply chain including:
(a) their name;
(b) the scope of their appointment;
(c) the duration of their appointment.

24. Changing the contract

24.1 Either Party can request a variation to the Contract which is only effective if agreed in writing and signed by both Parties. The Buyer is not required to accept a variation request made by the Supplier.

25. How to communicate about the contract

25.1 All notices under the Contract must be in writing and are considered effective on the Working Day of delivery as long as they're delivered before 5:00pm on a Working Day. Otherwise the notice is effective on the next Working Day. An email is effective (except for Legal Notices) when sent unless an error message is received.

25.2 Notices to the Buyer or Supplier must be sent to their address in the Order Form.

25.3 This clause does not apply to the service of legal proceedings or any documents in any legal action, arbitration or dispute resolution.

26. Preventing fraud, bribery and corruption

26.1 The Supplier shall not:

(a) commit any criminal offence referred to in the Regulations 57(1) and 57(2);

(b) offer, give, or agree to give anything, to any person (whether working for or engaged by the Buyer or any other public body) an inducement or reward for doing, refraining from doing, or for having done or refrained from doing, any act in relation to the obtaining or execution of the Contract or any other public function or for showing or refraining from showing favour or disfavour to any person in relation to the Contract or any other public function.

26.2 The Supplier shall take all reasonable steps (including creating, maintaining and enforcing adequate policies, procedures and records), in accordance with good industry practice, to prevent any matters referred to in clause 26.1 and any fraud by the Staff and the Supplier (including its shareholders, members and directors) in connection with the Contract and shall notify the Buyer immediately if it has reason to suspect that any such matters have occurred or is occurring or is likely to occur.

26.3 If the Supplier or the Staff engages in conduct prohibited by clause 26.1 or commits fraud in relation to the Contract or any other contract with the Crown (including the Buyer) the Buyer may:

(a) terminate the Contract and recover from the Supplier the amount of any loss suffered by the Buyer resulting from the termination, including the cost reasonably incurred by the Buyer of making other arrangements for the supply of the Deliverables and any additional expenditure incurred by the Buyer throughout the remainder of the Contract; or

(b) recover in full from the Supplier any other loss sustained by the Buyer in consequence of any breach of this clause.

27. Equality, diversity and human rights

27.1 The Supplier must follow all applicable equality law when they perform their obligations under the Contract, including:

(a) protections against discrimination on the grounds of race, sex, gender reassignment, religion or belief, disability, sexual orientation, pregnancy, maternity, age or otherwise;

(b) any other requirements and instructions which the Buyer reasonably imposes related to equality Law.

27.2 The Supplier must take all necessary steps, and inform the Buyer of the steps taken, to prevent anything that is considered to be unlawful discrimination by any court or tribunal, or the Equality and Human Rights Commission (or any successor organisation) when working on the Contract.

28. Health and safety

28.1 The Supplier must perform its obligations meeting the requirements of:

(a) all applicable law regarding health and safety;

(b) the Buyer's current health and safety policy while at the Buyer's premises, as provided to the Supplier.

28.2 The Supplier and the Buyer must as soon as possible notify the other of any health and safety incidents or material hazards they're aware of at the Buyer premises that relate to the performance of the Contract.

29. Environment

29.1 When working on Site the Supplier must perform its obligations under the Buyer's current Environmental Policy, which the Buyer must provide.

29.2 The Supplier must ensure that Supplier Staff are aware of the Buyer's Environmental Policy.

30. Tax

30.1 The Supplier must not breach any tax or social security obligations and must enter into a binding agreement to pay any late contributions due, including where applicable, any interest or any fines. The Buyer cannot terminate the Contract where the Supplier has not paid a minor tax or social security contribution.

30.2 Where the Supplier or any Supplier Staff are liable to be taxed or to pay National Insurance contributions in the UK relating to payment received under the Off Contract, the Supplier must both:

(a) comply with the Income Tax (Earnings and Pensions) Act 2003 and all other statutes and regulations relating to income tax, the Social Security Contributions and Benefits Act 1992 (including IR35) and National Insurance contributions;

(b) indemnify the Buyer against any Income Tax, National Insurance and social security contributions and any other liability, deduction, contribution, assessment or claim arising from or made during or after the Contract Period in connection with the provision of the Deliverables by the Supplier or any of the Supplier Staff.

30.3 If any of the Supplier Staff are Workers who receive payment relating to the Deliverables, then the Supplier must ensure that its contract with the Worker contains the following requirements:

(a) the Buyer may, at any time during the term of the Contract, request that the Worker provides information which demonstrates they comply with clause 30.2, or why those requirements do not apply, the Buyer can specify the information the Worker must provide and the deadline for responding;

(b) the Worker's contract may be terminated at the Buyer's request if the Worker fails to provide the information requested by the Buyer within the time specified by the Buyer;
(c) the Worker's contract may be terminated at the Buyer's request if the Worker provides information which the Buyer considers isn't good enough to demonstrate how it complies with clause 30.2 or confirms that the Worker is not complying with those requirements;
(d) the Buyer may supply any information they receive from the Worker to HMRC for revenue collection and management.

31. Conflict of interest

31.1 The Supplier must take action to ensure that neither the Supplier nor the Supplier Staff are placed in the position of an actual or potential conflict between the financial or personal duties of the Supplier or the Supplier Staff and the duties owed to the Buyer under the Contract, in the reasonable opinion of the Buyer.

31.2 The Supplier must promptly notify and provide details to the Buyer if a conflict of interest happens or is expected to happen.

31.3 The Buyer can terminate its Contract immediately by giving notice in writing to the Supplier or take any steps it thinks are necessary where there is or may be an actual or potential conflict of interest.

32. Reporting a breach of the contract

32.1 As soon as it is aware of it the Supplier and Supplier Staff must report to the Buyer any actual or suspected breach of law, clause 13.1, or clauses 26 to 31.

32.2 The Supplier must not retaliate against any of the Supplier Staff who in good faith reports a breach listed in clause 32.1.

`

33. Resolving disputes

33.1 If there is a dispute between the Parties, their senior representatives who have authority to settle the dispute will, within 28 days of a written request from the other Party, meet in good faith to resolve the dispute.

33.2 If the dispute is not resolved at that meeting, the Parties can attempt to settle it by mediation using the Centre for Effective Dispute Resolution (CEDR) Model Mediation Procedure current at the time of the dispute. If the Parties cannot agree on a mediator, the mediator will be nominated by CEDR. If either Party does not wish to use, or continue to use mediation, or mediation does not resolve the dispute, the dispute must be resolved using clauses 33.3 .

33.3 If the dispute is not resolved under clause 33.1 or 33.2, either Party may refer any dispute to be finally resolved by arbitration under the London Court of International Arbitration Rules current at the time of the dispute. There will be only one arbitrator. The seat or legal place of the arbitration will be London and the proceedings will be in English.

34. Which law applies

This Contract and any issues arising out of, or connected to it, are governed by English law.

APPENDIX A - VARIATION REQUEST FORM

Contract / Project Title: Contract / Project Ref No (FS /FSA No):
Full Description of Variation Request: A full justification and impact assessment including any supplementary evidence must be provided. Any supporting information should be appended to this form.
Area (s) Impacted: - Price ☐ Duration ☐ Price & Duration ☐ Scope of work ☐ Key Personnel ☐ Other ☐
Requester: Signature: Team / Organisation Date:
Supplier Contact Details Supplier Name : Contact Name : Contact Address : : Telephone No : Email Address :
FSA Use Only (Business Area) Amount Approved: Authorised By:- ☐ Cost Centre Manager ☐ Investment Board Signed : Date of Approval: **Please submit this form to** fsa.procurement@food.gov.uk

Procurement Use Only (confirm contract allows for requested variation) Variation Request No: Variation Request Approved by: Date of Approval:
On full approval of this Request for Variation, Procurement will produce a Variation Form for Contract and approval by both parties to append to the Agreement / Contract.

APPENDIX B VARIATION FORM

PROJECT TITLE:

DATE:

VARIATION No:

BETWEEN:

The Food Standards Agency (hereinafter called "the Client") & University of Birmingham (hereinafter called "the Supplier")

1. The Contract is varied as follows:

Contract x

2. Words and expressions in this Variation shall have the meanings given to them in the Framework.

3. The Contract, including any previous Variations, shall remain effective and unaltered except as amended by this Variation.

SIGNED:

For: The Client	For: The Supplier
By:	By: . . . . .
Full Name:	Full Name: . . . . .
Position:	Title: . . . . .
Date:	Date: . . . . .