National Measurement System scoping study

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NPL National Physical Laboratory

Ipsos

Contents

Glossary

BIVDA: British In Vitro Diagnostics Association

CHD: Congenital Heart Disease

CSR: Comprehensive Spending Review

DHSC: Department of Health and Social Care

DSIT: Department for Science, Innovation and Technology

FASP: NHS Foetal Anomaly Screening programme

FDA: United States Food and Drug Administration

HMT: His Majesty's Treasury (commonly referred to as HM Treasury)

IDBR: Inter-department Business Register

IEC: International Electrotechnical Commission

ISO: International organization for Standardization

Maryland SMS: Scientific Methods Scale

MHRA: Medicines and Healthcare products Regulatory Agency

MRIP: Medical Radionuclide Innovation Programme

NML: National Measurement Laboratory

NMS: National measurement System

NPL: National Physical Laboratory

R&D: Research and Development

RCT: Randomised Control Trial

SABR: Stereotactic Ablative Radiotherapy

SME: Small- and medium-sized enterprises

QALY: Quality Adjusted Life Year

QED: Quasi-Experimental Design

1 Introduction

1.1 Context

The National Measurement System (NMS) is key to delivering measurement science in the UK. It runs through a network of laboratories including the National Physical Laboratory (NPL), National Measurement Laboratory (NML, hosted by the LGC Group) and National Engineering Laboratory (NEL). These laboratories provide world-class measurement science and technology which is essential to improving the productivity and prosperity of the UK. They do so through developing and applying measurement standards for accurate scientific and technology readings and through ensuring integrity and quality in measurements and in cutting-edge measurement technology. This contributes to novel technology development and innovation.

The NMS focuses on major societal challenges, through the set-up of challenge areas which sit across measurement science functions. There are major opportunities and challenges in the life science and healthcare sectors, both in terms of healthcare delivery and also in applying expertise to health and life sciences research. In addition, there are fast-moving developments in the life sciences sector including in the development of medical devices, diagnostics, and pharmaceuticals. Given this, the top-level management of the NMS is structured around a series of challenge areas, of which one is ‘Life Science and Health’. Through this challenge area the aim of the NMS is to improve measurement standards and methods across healthcare. This will contribute to new developments in healthcare technologies and improvements in the delivery of healthcare services while helping to reduce the cost of healthcare.

The next Comprehensive Spending Review (CSR) round is due to take place over 2024, following the previous CSR in 2021. It is a key process within the government's strategy for allocating public funds conducted by HM Treasury (HMT). It involves a thorough evaluation of the government's multi-year spending plans and commitments, to determine the efficiency of public funding. NMS activity and impact will form part of the review, which NPL and NML will both need to prepare evidence for.

Due to the timeframes of the scoping exercise, and the expected timeframe for the CSR, it is necessary to focus on activities where it is possible to quickly gather the evidence available that supports arguments made as part of the review. It will not be possible to capture the full breadth and depth of scientific activities underway across the NMS along with all the benefits associated with each. This would require a much more detailed study approach and may not clearly prioritise the benefits that the audience for the CSR expects to see. The audience for the review

process will be economists and analysts at the Department of Science, Innovation and Technology (DSIT) and HMT. This audience will look for certain principles in topic areas where there is greater evidence of impact, such as understanding where there is cause and effect from NMS activities to provide measurable economic and social welfare benefits.

1.2 Scoping study aims and objectives

Ipsos were commissioned by the NPL in November 2023 to undertake a comprehensive scoping study to explore potential opportunities and study options to measure the impact of activities within the NMS on Life Science and Health. The purpose of the exercise has been to explore and present a selection of short-term study options, which NPL and NML can take forward in advance of the CSR process, as well as two further options to undertake longer-term studies.

The objectives of the scoping study have been to:

1. Set out, at a programme level, how the NMS achieves impact through the development of a Theory of Change (ToC) setting out pathways to impact;
2. Appraise options for generating evidence across the different pathways and activities of the NMS; and
3. Shortlist four short-term studies to develop study plans and practical details around aspects such as data sources, methods, and capabilities required. The NPL and NML will have the opportunity to then take these four studies forward in preparation for the CSR. Alongside this, the study will shortlist two longer-term studies that can contribute to future business cases.

Given the nature of the work, this was by large a development exercise. Final decisions regarding the impact evaluation work to be undertaken lies with NPL and NML and will depend on specific emphasis of the future CSR and any business cases NPL and NML wish to put forward. Therefore, there will likely be a need to adapt the study proposals set out in this paper.

2 Conceptual Framework

2.1 Challenges for assessing impact

The nature of the NMS poses challenges to measure impact. There are a variety of activities across the system which broadly fall into the following categories:

1. Collaborative Research with Medical and Clinical Researchers
2. Collaborative Research with Commercial Developers (Commercial R&D)
3. Technical Consulting and Advisory Services to the NHS
4. Knowledge Transfer and Training

Each group of activities leads to different benefits in the Life Science and Health sectors, including the development and adoption of standards, commercial and economic growth among manufacturers, patient health benefits and health system savings. Across all of these activities and types of benefit, there are several challenges to assess:

- Some NMS benefits might only be realised in the very long-term. Evaluations will need to focus on capturing progress towards long-term benefits. For example, research activities often take time to progress through intermediate outputs such as publications, citations, patent applications and registrations. The adoption of traceable standards by companies and international organisations can take several years. Of the research areas and technologies covered across the NMS, many are early-stage research, although some other topics have historically been well- established with evidence of benefits available going back over several years.
- Some NMS activities, such as improvements in measurement and methods, must be translated and rolled out in the NHS and wider life sciences sector for wider economic and health benefits to be realised.
- NMS activities may be only one contribution of many to the improvements taking place. For example, research to improve diagnostics and medical devices will draw on several subject areas, of which research into device measurement is one of many subjects and implementation depends on a range of activities by equipment manufacturers too. In settings where counterfactual or quasi-experimental methods are not viable, this will raise challenges in disentangling the incremental benefits of NMS activities from those of other programmes.

- A robust assessment of economic impacts, for instance on commercial manufacturers of medical equipment, would ideally need to identify comparison groups of firms. These firms must not have collaborated with NMS and must not have been spun out from NMS programmes. As it is the case that many NMS research outputs are adopted into regulatory standards and approvals for new products, there are often no manufacturers that are unaffected by the work of the NMS and thus there is no suitable counterfactual group.
- Opportunities to model the wider health and wellbeing benefits of NMS activities will have to consider both materialised and future benefits. Modelling future health care system savings, monetisable improvements in Health-Related Quality of Life and wider health benefits will have to be based on the current risk and prevalence of major long-term conditions, depending on the specific nature of NMS training, knowledge sharing and collaboration activities with clinical teams. This implies the need to work with expert stakeholders to firstly establish reasonable assumptions on the most likely areas of disease that have or will benefit from, for example, improvements in radiotherapy, diagnostics, and medical imaging; and secondly establish the likelihood of improved diagnosis or treatment as a result of the NMS activities.

2.2 Rationale for selecting a theory-based conceptual framework

As part of spending decisions, the preference of HMT is to, where possible, consider evidence which scores highly on the Maryland Scientific Methods Scale (SMS). Such evidence demonstrates a causal impact and aligns to the spending decisions the CSR will take. The hierarchy for study designs is as follows:

1. Randomised Controlled Trials (RCTs): gold standard trials which provide the strongest causal evidence by randomly allocating subjects into treatment (those who receive the intervention) and control groups (those who do not receive the intervention). The randomisation approach potentially eliminates any observable or unobservable differences between the groups, meaning that any differences in measured outcomes between the two groups can be reliably attributed to the intervention. This scores as 5 (the highest available score) on the Maryland SMS.

2. Quasi-Random Studies: These trials include designs where the allocation to treatment is not strictly random but is based on a rule which can mimic random assignment at the margin. This scores as 4 on the Maryland SMS.

3. Quasi-Experimental Designs (QEDs): Situated below RCTs and quasi-random studies in preference, QEDs do not involve random assignment but still provide valuable causal evidence through careful construction of comparison groups and controlling for potential confounders in the analysis of differences in outcomes between the treatment and control groups. This will typically score as 3 on the Maryland SMS.

The challenges set out in section 2.1 highlight the core challenge for measuring the outcomes and impact of the activities of the NMS. The upstream research work the NPL and NML undertake themselves is observable, and it is within their control to design studies for their own activities that score highly in the Maryland SMS. However, the wider health, economic and societal outcomes of these activities take place further along a causal chain. Demonstrating that NMS activity is leading to downstream benefits is of primary interest to government, however it is difficult to measure or control these downstream changes where the causal chain is weaker. It becomes increasingly difficult for the NPL and NML to have sight of or control over what is taking place, which limits the ability to undertake the above types of study.

Given this, in the majority of cases it is not possible to undertake a counterfactual study. The same limitation applies across multiple other government programmes, such as government Industrial Strategy Challenge Fund programmes where there is not a clear way to identify a comparator or separate out different actions being taken. The above study designs also require reasonable sample sizes to allow for tests to be carried out on data with sufficient statistical power, programmes to be designed to randomise users into a clear treatment and control group, or – for QEDs – for the programme to identify a suitable counterfactual group. Randomisation will need to feature in the intervention from an early stage, where it is ethical to do. In the case of the NMS there are very few circumstances in which these conditions hold. Due to the complexity of the work that the NMS carries out, it is also difficult to ascertain whether causal impacts can be directly attributed to the NMS inputs unless the programme and its stakeholders (such as the NHS) hold extensive relevant data.

For this reason, it is important to consider assessing the contribution of the NMS to its desired impact using **theory-based methods** which are more viable than using statistical counterfactual methods. Our rationale for choosing a theory-based approach is that through extensive consultation with the programme, it is possible to build and test an evidence base for the programme by setting out its pathways from inputs, activities, and outputs through to outcomes and final impact.

In principle it may be possible in future evaluations of NMS interventions to undertake a RCT or QED approach, for instance by implementing new tools across NHS Trusts or stakeholder organisations in a phased manner, allowing organisations which adopt the new tools later to serve as a counterfactual to the earlier adopters. However, this may not be practical due to ethics approvals, implementation being out of the evaluation team's control, or long timescales before an impact is observable.

2.3 Theory of Change

Through consultations with staff across the NMS and through reviewing key programme documentation, the scoping study team developed a Theory of Change (ToC) setting out the programme's pathways to a variety of economic, health and wellbeing impacts. This ToC underwent consultation and review with relevant staff across both NPL and NML. From left to right the key components in the ToC are:

Inputs: resources necessary for the operation and success of the NMS, including staff, finances, and equipment. This also includes funding and stakeholder input including from government and industry.

Activities: actions or tasks undertaken using the inputs. These are grouped as the four activities set out in section 2.1.

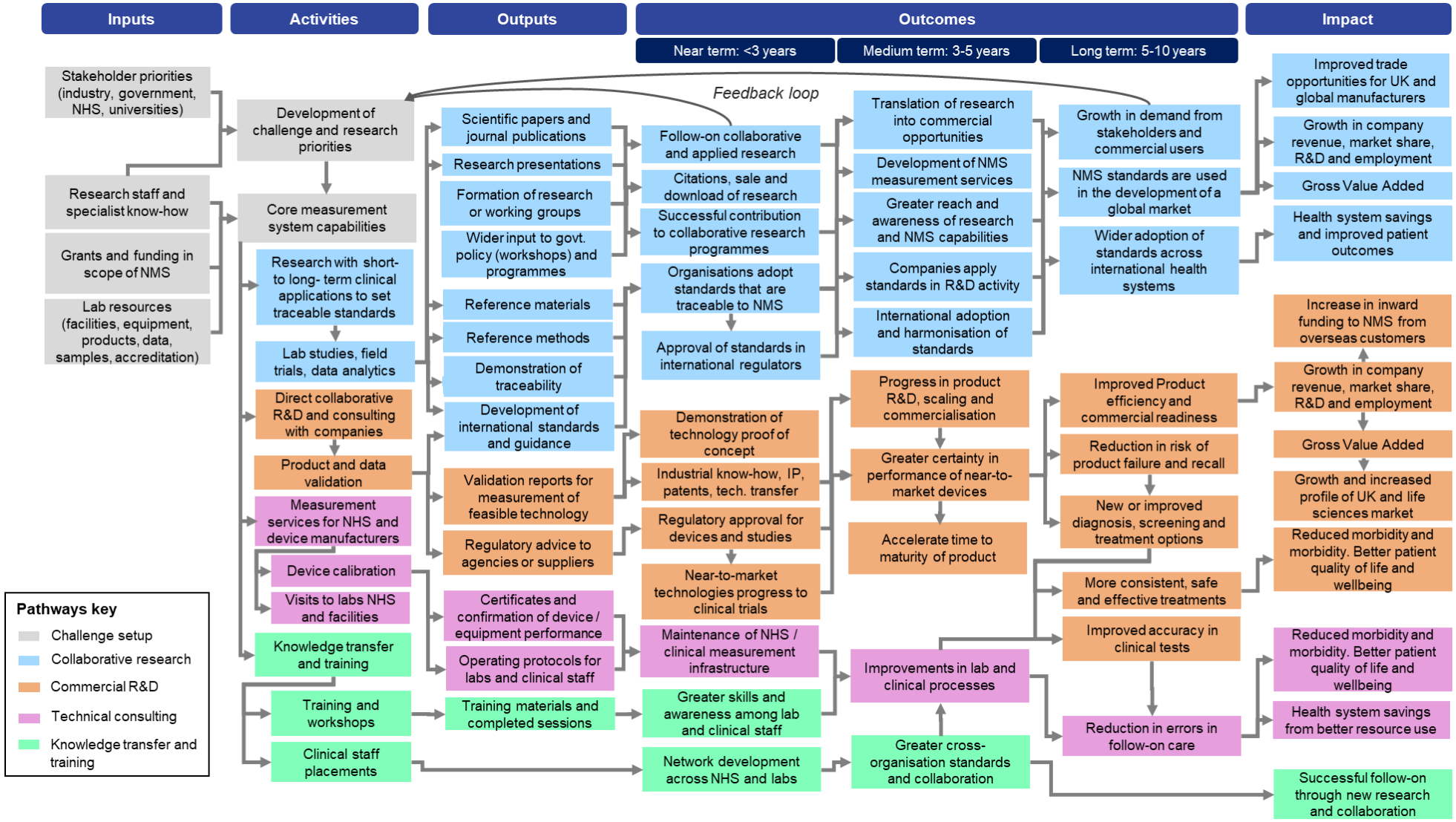
Outputs: immediate, tangible results of the activities that organisations in the NMS have produced. In the context of the NMS, this includes new research resources, publications, protocols, validation reports and completed sessions with key stakeholders such as NHS staff.

Outcomes: results which emerge beyond the immediate programme deliverables with wider benefits or implications beyond the NMS. These can range from short-term (such as immediate adoption of standards) to long-term (such as progress in developing a new technology).

Impact: the potential or anticipated end-results from the NMS, including with respect to economic growth, end-user (patient) benefits from using newly approved technologies, improved population health outcomes, and reduced health inequalities.

Following a workshop and follow-on consultation with staff across the NMS, the ToC is set out with each of four *pathways to impact* (overleaf). It sets out clear hypotheses for how change happens, through setting out causal pathways to impact with underpinning assumptions.

Figure 2.1: National Measurement System programme Theory of Change (ToC)



2.4 Contribution Analysis

To test the impact of the NMS on Life Science and Health, *Contribution Analysis* is a viable method for considering and testing evidence drawing on the pathways and impact set out in the Theory of Change. Contribution analysis can interrogate pathways in the Theory of Change and assess the extent to which observed outcomes occur due to the NMS rather than other external factors. A typical approach is to collect quantitative and qualitative evidence on overall impact, and then work backwards from the impact to test NMS causal mechanisms and contribution, alongside other factors, against the Theory of Change.

This involves testing in detail the assumptions that contributions to the programme make, as well as alternative explanations for why certain outcomes and impacts have materialised. All data and methods, both qualitative and quantitative, can inform a Contribution Analysis, to collect evidence in favour of or against contribution claims. In this process, contribution claims are not validated or discarded. Rather, they are progressively fleshed out, for example from “the intervention contributes in such a way” to “when conditions x and y are met, the intervention contributes in such and such a way, unless event z occurs”, leading to “causal packages” that bring together several factors associated with observed changes. Study approaches that build out from a contribution claim can bring together a variety of evidence sources to generate impact evidence while also providing supporting narrative that builds out from key points and assumptions within the contribution claim.

The technique can confirm the plausibility of the hypothesis that an intervention (such the operation of NMS) has had a material role in bringing about a particular outcome or impact. In some cases, the assumptions on causal links in the contribution claim can be further tested through *process tracing*, which would use evidence sources to map out each link.

The main drawback of contribution analysis is its potential for confirmation bias, i.e. the risk that the analysis confirms the prior beliefs of the evaluator conducting it. The approach also requires a certain level of evaluator judgement which can sometimes happen without peer review. To mitigate these, an “open book” approach to analysis can be chosen, stating evaluators’ prior beliefs about certain programme contributions explicitly, and updating these throughout evidence gathering in a manner that is transparent and can be interrogated by key stakeholders.

For each of the study options identified through the scoping exercise in Section 4 of this report, a Contribution Analysis approach is set out as – in the absence of RCT or QED approach, and

with the time available before the CSR – this presents a pragmatic way to test and collect evidence against potential claims of impact for the NMS.

2.5 Focusing in on topic areas

It is not possible to capture the full breadth and depth of scientific activities underway across the NMS, However it is possible, and ideal in preparing for the CSR, for both the NPL and NML to focus in on specific topics where there is a strong potential to measure impact from long-standing activities and government policy interest. As part of the scoping exercise, conversations in February 2024 with teams across NPL, NML and DSIT took place to explore the labs' scientific activities in more detail. This included a wide range of novel and established research areas. The topics identified to consider further :

- Radiotherapy (radiation dosimetry)
- Radiopharmaceuticals
- Ultrasound testing
- Nanotherapeutics
- Molecular diagnostics
- Data Science

Appendix 1 sets out details on additional topics which were not prioritised as part of the scoping study.

3 Study Options Appraisal

3.1 Overview of options appraisal

For all of the six topics set out in section 2.5, the study team identified that there were multiple possible outcomes or impact that study approaches could consider. This included exploring different clinical specialities or pathways (for instance, within the radiopharmaceuticals and nanotherapeutics topics, it is possible to explore both the diagnostic and therapeutic applications of NMS research) and different impact pathways the Theory of Change (for instance, exploring company growth or patient benefits).

To appraise different study options within each topic, an options appraisal session took place in March 2024 with staff across NPL, NML and DSIT. In the absence of pursuing a RCT or QED approach, the options appraisal set out a mix of quantitative and qualitative methods and evidence sources which could be applied to test a contribution claim. The Ipsos scoping study team presented a contribution claim for each topic, along with various assumptions, data and methods which could test the claim. This led to a discussion on which aspects of the claim and methods were most important to test and take forward.

Potential evidence sources considered across each topic included: company data, interviews, expert input from stakeholders, reviews of research evidence, reviews of audit data, process mapping, modelling or simulation approaches and qualitative case studies. The preference of the group to pursue a particular approach varied by each topic and considering which study approach to prioritise depended on multiple factors:

- The nature of the economic or patient benefits that the contribution claim could focus on.
- The types of companies the NMS works with or influences in each topic area, including their size and country of operation. For the CSR, it is necessary for studies to focus on benefits for UK residents and UK-based companies.
- The stakeholders best placed to test the contribution claim and provide expert input.
- The time necessary to generate evidence, and whether the topic is better suited to conducting a short-term or long-term study.
- How the topic aligns with government policy priorities.

The aim of the options appraisal workshop was to prioritise **four small, short-term studies (section 4 of this report)** and **two longer-term studies (section 5)** among the topic areas, considering where there is the greatest opportunity to generate evidence.

3.2 Summary of appraisal discussions

Each topic area discussion was unique based on the nature of the supplier market, the nature and timescale of benefits, political interest, and known opportunities to partner with or gather data from stakeholders. This revealed preferences on how to take forward each topic:

- **Radiotherapy**: The group agreed that a study focusing on radiotherapy instrument manufacturers would not have been useful for the CSR as most manufacturers operate outside the UK, with companies such as Varian, Elekta, Accuray and Siemens based across the United States and Europe. For the CSR, it is necessary to focus on growth in companies which are UK-based. By contrast, there is a more direct and measurable contribution from the NPL to NHS radiotherapy departments through its measurement services, which work with the NHS to support safe and effective radiotherapy delivery for patients. Through this, it is possible to measure the impact of the NMS on NHS patient health benefits such as through improving cancer outcomes. Improving patient cancer outcomes is an ongoing priority for the NHS.
- **Radiopharmaceuticals**: The group considered opportunities to focus on either the downstream commercial benefits or patient benefits from manufacturers of radiopharmaceuticals adopting measurement standards from the NPL . These standards allow manufacturers to reach regulatory approval and commercialise novel medical products. The group discussed whether it would be preferable to focus on the potential patient benefits from greater access to diagnosis or treatment options, or company growth. A study focusing more broadly on commercial growth and investment trends across radiopharmaceuticals manufacturers was chosen, where data is available for these manufacturers among Small and Medium-sized Enterprises (SMEs). By contrast, a study focusing on specific patient benefits would likely have been focused on a more specific clinical use-case or pathway.
- **Ultrasound:** The group agreed that a study on ultrasound device manufacturers would not have been useful for the CSR as most manufacturers are not UK-based. In focusing on patient benefits, the group also agreed that it did not make sense to design a focus on dosage and safety, along the same lines as a study on radiotherapy, as ultrasound devices do not require routine calibration from NPL measurement services on a regular basis. As an alternative, the group discussed that there is good publicly available data and policy interest on NHS foetal ultrasound screening and the potential benefits of improvements to NHS screening programmes. Foetal ultrasound is a large proportion of the total annual activity for ultrasound services.

- **Nanotechnology:** The group discussed different technologies to focus on within this topic area. This included discussion of nanomedicines and nanotherapeutics at early to late stages of development respectively. The NPL and NML have a track record in undertaking research for measuring many established nanotechnologies in healthcare, which could form part of a near-term study on the benefits of NMS for companies developing and commercialising nanotechnologies. The highly varied application and benefits of nanotechnologies across different clinical use cases meant that it was more practical for the group to focus more broadly on commercial benefits for companies. The group also discussed that a separate longer-term study can instead focus on the role of NMS staff in influencing international standards to support the UK in R&D for earlier-stage or more novel nanotechnologies. This does not need to take place in time for the CSR and can take additional time to demonstrate how the NMS is currently representing UK industry in conversations with international standards bodies.
- **Molecular diagnostics:** The group discussed the opportunity to focus on the NMS contribution to developing new standards and regulatory protocols for reviewing and approving diagnostics for COVID-19 during and after the COVID-19 pandemic. There was consensus to explore an approach that would map out changes and improvements in processes for regulating new diagnostics before and after COVID-19. The group also discussed that this is best suited to a longer-term study as the fast, emergency response nature during the pandemic itself meant that many standards have taken time to put in place in retrospect. As a result, it is preferable to explore this study beyond the CSR and monitor progress in implementing regulatory processes that are underway, or future improvements in regulating molecular diagnostics that are still expected to take place.
- **Data Science:** The group discussed a specific data science project, in which the NPL worked in partnership with a local NHS Trust, as a potential case study. The group agreed, however, that the case study presented was not right to use it did not focus clearly enough on measurement science and on the additional capabilities the NMS can provide. This topic was therefore not taken forward at this stage. An alternative case study was not identified following the options appraisal.

Where, as a result of deliberation with NPL and NML, topics were not taken forward at the Options Appraisal stage or an earlier stage, these are also set out in **Appendix 1** for any future reference.

4 Short-term study plans

The short-term study plans were devised considering that the studies which we are suggesting are inevitably – and will remain – developmental in nature. The study approach will need substantial adaptation in the light of what data and evidence emerges, and thus these plans are intended to provide an initial roadmap within the available timescale and resources. Due to the lack of a clear counterfactual study design, there will need to be considerable adjustment and consultation with a range of experts based on the findings and quality of evidence that emerges and based on the timeframes to generate evidence against the CSR. Initial feedback provided by NPL and NML science team members has suggested that the suggested approach to particular topic areas does not appear to offer the potential level of certainty they would want to see. However, the immediate goal of studies developed for the CSR is to strengthen the impact evidence that NPL and NML could use during the CSR process and in any other near-term submission of business cases, rather than to provide total certainty for the topics, which is likely not feasible.

4.1 Radiotherapy patient benefits

4.1.1 Overall approach and nature of evidence generated

Accurate radiotherapy administration is essential for effective cancer treatment and minimising patient harm. Errors in radiation dosage can reduce the effect of treatment on the tumour or increase the risk of adverse effects on healthy tissue. This study aims to estimate the patient benefits resulting from the reduction in radiotherapy administration errors and drift from the correct dosage, which the National Physical Laboratory (NPL) enables through audits of radiotherapy equipment and measurement services. This work considers the **Technical Consulting** pathway within the Theory of Change.

The radiation dosimetry team at the National Physical laboratory has previously supervised a medical physics PhD student, using their outputs with economics colleagues to undertake a similar exercise. While there have been prior challenges in studying impact in this topic area with a high degree of certainty, it is possible to focus in on this work – in the short term – in such a way that it generates key evidence or assumptions for the purposes of testing a relevant contribution claim.

In the time available before the CSR, the proposed study will explore the opportunity to develop, gather evidence for and run a simple decision model to estimate patient benefits from receiving the correct radiotherapy dose. The model will run on the assumption that NPL is providing these

services, versus a case where another organisation with a higher error rate provides the services. The model parameters will be set using measurement audit data from the NPL or, in the absence of audit data, expert input and research evidence. Developing a complete model will be a significant endeavour that is likely to require additional time later in the year beyond the CSR. Therefore, the chosen study team should approach this topic pragmatically to consider how it develops an initial model, and in the first instance which model inputs, assumptions, data or expert input can best support the contribution claim while working towards this as a longer-term goal.

The model will consider the degree of error, or drift, from the correct dosage which would be likely in the absence of NMS measurement services work and audits, as well as research evidence or clinical expert input on the effect of high dosage on patient harm and the effect of too low or high a dosage on the response from different types of patient tumours.

Findings from the modelling will provide insights into the impact of accurate radiotherapy dosage on patient outcomes (patient survival and quality of life) and the role of NPL's measurement services in ensuring the safety and effectiveness of radiotherapy treatments. To set out meaningful assumptions in a short timeframe, the approach will likely need to focus in on a specific tumour or patient type as a case study. The approach will also need to pragmatically consider available evidence or documentation within the timelines necessary for the CSR.

Contribution claim

- **If…** specialists validate radiation dosage in NHS and pre-clinical settings, to ensure that the dosage of existing and new types of radiotherapy treatment are correct
- **Then…** the successful implementation of measurement services and standards will identify errors in existing radiotherapy devices already in use in hospital settings or lead manufacturers to improve their calibration of new devices
- **This will lead to…** a reduction in dosage errors, enhanced safety, and effectiveness of radiotherapy procedures, with more consistent delivery of treatment across all NHS patients
- **Ultimately…** the result of this consistency and reduced margin of error will lead to a significant increase in the quality of life and life expectancy across the cohort of patients undergoing the procedures.

The nature of benefits in this proposed study are to be modelled on historic data and assumptions. Feedback from the NPL radiation dosimetry team also suggests that this same modelling approach can consider prospective benefits from the introduction of new technologies in some specific clinical use cases, however the study proposed here prioritises the reduction of errors through well-established measurement services. One of the broader challenges in considering the impact of these services is that, so long as they function as intended, there will be few, if any, observable errors in the delivery of radiotherapy doses. It then becomes more challenging to demonstrate what difference the service has made. To overcome this and take into the account the direct activity NPL undertakes, it is possible to use this type of study approach to make comparisons to the measurement work of an international peer or supplier of calibration services in terms of the relative cost and quality of service they provide. It may be also possible to highlight or draw on historic case study examples where an error has been applied. For instance, while uncommon, the NPL is aware of incidents in which patients have received the wrong radiation dose. There is some potential to use examples to draw further assumptions around the potential harm of dose errors if these were to be repeated.

4.1.2 Methodology

The project will employ a modelling approach to estimate patient benefits from the reduction in error of radiotherapy administration. The model will be developed using the following steps:

1. **Topic selection:** There is considerable variation in how dose will affect different groups of patients based, inter alia, on their tumour type, stage, and location. Focusing in on a specific sub-group of the patient population will allow for analysis to take place more manageably in a short timeframe and with a more meaningful degree of specificity. This is necessary to avoid using generic or averaged assumptions on the relationship between the delivery of radiation dose and patient benefits. One such audit of dose in a speciality area suggested by the radiation dosimetry team is lung treatment delivery measured through SABR (Stereotactic Ablative Body Radiotherapy). It is, however, important not to lose sight or other clinical specialities or tumour types where there may also be benefits from improved radiation dosage – it is helpful to report where there may be wider benefits applicable even if these are not as practical for quickly generating evidence.

2. **Model identification:** The study team will research and select the preferred modelling approach. After defining a clear patient group (for instance, the SABR example above), and health outcome (patient longevity and quality of life over a set 5- or 10- year timeframe for patients) other key model principles can be considered. The exact model approach and

structure will relate to the decision problem the model is addressing. In this case, key considerations are:

Comparator: While a true QED approach is not possible given the challenges referenced above in section 2, one suggestion is to consider the rate of error identified at other National Measurement Institutes where information of the relative performance is available, relative to the rate of error from services NPL provides. Understanding the rate of error for a comparator should take place with consultation from the NPL radiation dosimetry to help guide how best to set assumptions drawing on known risks or incidents that may arise in the absence of an ongoing measurement service or audit process.

Model structure: Due to the nature of the decision problem relating to radiation dose, it is necessary for the model structure to include different elements. Firstly, it will need to simulate that a patient (or cohort of patients) can receive a range of potential doses, and then provide a structure following on from this that considers how they experience differing health states over time that are associated with the doses they received. As the dose the patient receives follows a probability distribution, an initial statistical or simulation model would draw dose values from this probability distribution. Patients will typically receive multiple courses of treatment over multiple weeks depending on the specific treatment. For each course of treatment, the model will draw a new dose value from the distribution. If the model considers a cohort of patients (for instance, the total number of patients expected to receive SABR in a given year) then a dose amount will be drawn for each patient for each course of treatment. This is likely to use a probabilistic or statistical model.

Modelling radiotherapy dose accuracy is complex in itself due to factors such as tissue heterogeneity, patient anatomy, internal organ motion during treatment delivery, characteristics in the beam and other factors related to the treatment of patient biology. Expert advice should be sought with the NPL Radiation Dosimetry team on the most suitable approach to take, whether any specific examples of healthcare delivery are more certain or better suited to develop a model on dose and whether there is any pre-existing work that the team can draw upon. It is also essential that the study team prioritises quick and practical approaches that allow it to focus on measurable benefits to patients – which is where HMT and government interest will be for this exercise. If there are more approximate approaches to consider what the probability of error is, for instance through using counts from past reports of incidents with patients, it may be preferable to provide an

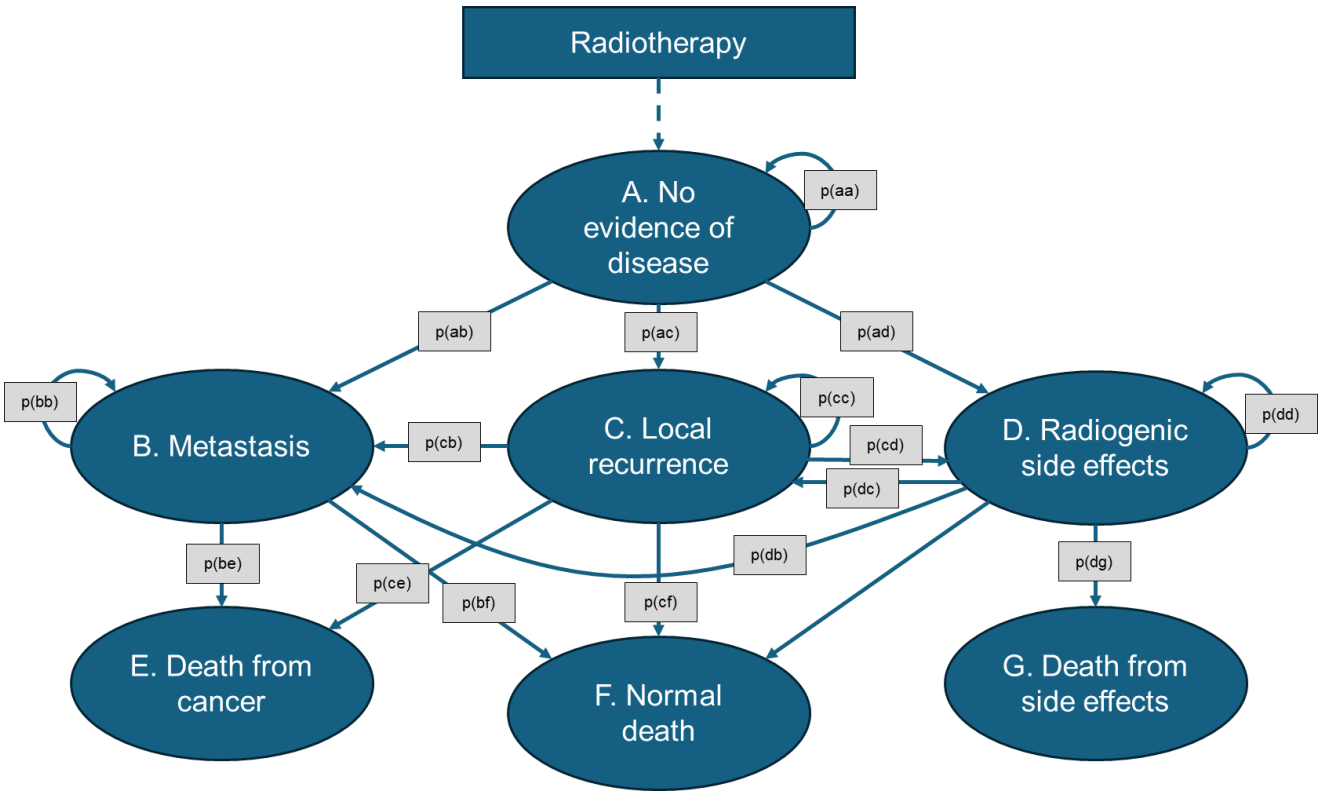
initial ‘rule of thumb’ probability of error. There will then be further opportunities to expand beyond this following on from the CSR.

Secondly, the dose the patient receives would then need to affect the probability with which they progress from their current health state into an improved health state (for instance, remission) or deteriorated health state (either due to receiving a low dose, or due to developing secondary complications from a high dose). Due to the recurring nature of the treatment and long timeframe over which patients could transition between health states following the treatment, a *Markov health state transition model* is a sensible choice to ensure that patient quality of life and benefits are measured. This is a common health economic model structure in a wide range of healthcare applications.

The probabilistic model will likely be mathematical and use a programming software such as MATLAB, Python or R. The Markov model will typically be visualised and then run in a software such as TreeAge, Excel, Python or R.

Example illustrations of the Markov model structure is below:

Figure 4.1: Example illustrative *Markov transition model* structure for a radiotherapy dosage use case – each oval represents a health state that the patient or cohort of patients enter at a discrete point in time. These will each have an associated quality of life from full health / high quality of life to low quality of life and death. There is a probability (transition probability) assigned to the likelihood that a patient moves from one state to the other based on their course of treatment. These probabilities may be varied according to the precision / effectiveness of the course of radiotherapy treatment received.



Source: Recreation of figure from *Xie, Guo and Zhang (2020)* Cost-effectiveness analysis of advanced radiotherapy techniques for post-mastectomy breast cancer patients

Depending on chosen structure, the study team will need to consider more detailed factors when setting up the model. For instance, which 'buckets' of health states are most appropriate for the patient to move between.

3. **Define and complete input parameters:** For either model structure, a set of underlying assumptions will be important to consider building into the key model parameters. For instance, the probability that a patient moves between health states due to an error in dose will vary based on the likely effect of dose on patient health. An overall set of assumptions to consider, which feed into the model structures, include:

   - The number and grouping of patients treated by cancer type, for the topic selected.
   - The length of time patients receive treatment courses for.
   - Reported patient survival and quality of life for the tumour type.
   - The degree of error or drift from the correct dosage which would arise in the absence of the radiation dosimetry service.

- The frequency with which drift in device accuracy occurs, or time over which drift from accurate readings occurs.
- The effect that high dosage has on patients becoming more likely to experience harm or recovery over time owning to tumour response or secondary harm caused.
- The cost of the radiation dosimetry service NPL provides as opposed the cost of the service other measurement institutes provide.

The study team will consider model input parameters and distributions through a *review of the available data*, *review of research papers*, and *interviews with experts*. If access to peer data allows, this approach can also consider input parameters for a potential peer organisation to act as a comparator. The NPL radiation dosimetry team will be important to consult on key assumptions and comparisons drawn to peers.

4. **Calculate and analyse results:** Having set model assumptions and parameters, the study team will run the model to identify any differences in patient longevity and health outcomes due to NPL providing the service.

   To better measure uncertainty and generate a range of potential outcomes, both models can apply a probabilistic approach through building in a Monte Carlo simulation. This approach will allow the study team to create a distribution for some variables which they wish to sample or test the uncertainty of. Distributions for any variable under simulation will be specified based on evidence the study team can gather. This can run over several iterations (e.g., 10,000 or more scenarios which are different draws of parameter values from the distributions defined in step 3) to generate model results that are attentive to any potential uncertainty in the model assumptions.

   There are other instances where researchers have applied health economic modelling to a similar use case to radiotherapy delivery. A small number of illustrative examples are set out in **Appendix 2**. Other studies will typically follow on from RCT or observational studies. While the data source and approach from this study differs, these studies still serve as an illustration of the method in practice. These studies also do not focus on modelling dose error in the same manner as NPL will do through this exercise.

5. **Summarise results:** The study team will report overall outcomes from across all the scenarios run. This will cover overall changes in lifespan or quality-adjusted life years (QALYs) for the cohort of patients relative to the comparator. It will also include sensitivity analysis results to capture any uncertainty in the assumed outcome distributions. For the

timescales and purposes of the CSR, the study team will have to adapt and consider, carefully, how a simplified or early version of the model and its assumptions – based on analysis of data and expert testimony – feed into the Contribution Analysis approach.

6. **Expert validation:** The model and its findings will be validated through consultations with clinical experts and researchers.

4.1.3 Data sources

Key model parameters and assumptions will not be readily available and require a mix of expert consultation and examination of available research outputs, along with audit data available to the NPL. Key resources which the NPL should consider include the following:

Source	**Type of data**	**Key considerations and access requirements**
Radiation dosimetry audits	Data on improvements in device calibration	N / A – consult with the radiation dosimetry team at NPL
PubMed, Cochrane Library, ClinicalTrials.gov	Research portals which provides access to a database of citations and abstracts across medical fields to enable review of literature for potential assumptions, as part of literature review approaches	Full texts of articles may require a subscription or purchase from the publisher; however, some articles will be available through PubMed Central. It should be considered that the team conducting the work budgets for or can access articles
NHS Cancer Data – https://www.cancerdata.nhs.uk	Summary level information on the number and type of cancer diagnosed. While more specific information from a review of the above research portals will be necessary to focus on specific population groups	Summary data is open to access online

	and case studies for radiotherapy, the information here can provide summary details on the number and types of patients diagnosed with cancers, and quality of life	

The above modelling approach will need to draw on research evidence sources. This will include one or more of the online clinical research portals cited in section 4.1.3 to better understand the relationship between radiation dose and health, and radiation dose and cancer response. While they may not form part of the core team, forming routine touch points with expert researchers in the fields of radiation dosimetry and oncology will allow the team target relevant literature and form a view on early assumptions. Similarly, this stakeholder group can help to draw out and make sense of research outputs. Discussions with experts should follow a structured interview approach to explore the impact of high and low doses on patient outcomes under varying circumstances. Adopting a structured approach will help to generate model assumptions and parameters in circumstances where there is uncertainty.

Summary-level data on the number of patients by cancer type and type of radiotherapy administration may provide overall figures on the number and type of patients with cancer types, and their reported quality of life, to include in the study approach. However, given the focus of this study will likely cover a specific population group with a specific tumour type, it is recommended that more detailed model assumptions form part of a literature review. More detailed patient level data held by NHS England will require a Data Access Request which will take additional time to request.

The National Physical Laboratory holds information from dosimetry audits, covering both reference dosimetry for various modalities and end-to-end audits for advanced radiotherapy techniques. The frequency of these audits is variable and depends on factors such as the specific type of audit and whether it is conducted on-site. Audit data has formed part of prior work the NPL has published on improvements in dosimetry (online here).

4.1.4 Indicative timeline

The timeline presented here is indicative and considers only the run up to the CSR, with a view that the study team will need to be pragmatic to generate evidence quickly, and adapt the approach based on the type of evidence arising.

In anticipation of the CSR, the study will need to generate and report headline findings over a short 3-to-4- month period. This will require fast gathering of evidence and analysis. In **month one** the team should prioritise project planning, agreeing principles for the simulation approach, setting a scope for analysis of audit data and review of external research evidence, onboarding additional modelling specialists, and inviting experts to interview.

In **month two** the team should focus on defining a model structure and executing a quick and pragmatic document review, analysis of NPL audit data, and conduct staff interviews. These actions together will enable the team to establish initial estimates for model assumptions and parameters set out in section 4.1.2. While undertaking these reviews, the team should also pragmatically use evidence to test the contribution claim.

In **month three**, the team should construct an initial and simple version of the simulation model using model parameters, seeking regular input from experts and the NPL radiation dosimetry team to build on previous work. The model analysis ought to report on differences in patient life years and quality of life relative to a comparison rate of error. The team should draw out, from data and expert opinion, assumptions for a comparable Measurement Institute with a higher rate of error for the measurement service it provides.

In **month four** the team should summarise and write-up initial analysis findings, providing a headline difference in patient outcomes. This difference will contribute to Green Book approved measurements of monetisable health benefits. Any wider narrative which comes from expert commentary and interviews, and any refinements to the contribution claim should also feature. Where there are high margins of uncertainty in the model outputs the team should prioritise testing the contribution claim by developing narrative using its analysis of data, literature, and expert opinion to demonstrate the expected difference between the NPL service and the comparable service elsewhere.

4.1.5 Key risks to manage

There are several key risks to manage across the study:

- One of the key assumptions the study must capture is the relationship between patient dose and outcomes. These are captured through Tumour Control Probability or Normal

Tissue Complication Probability curves. However, feedback from the radiation dosimetry team suggests there is not a consensus for the shape of many of these curves. Understanding whether a dose is accurate and safe is complex and relies on multiple factors relating to the patient and the course of treatment. Focusing the study too generally will also make it more difficult to establish what the relationship between dose and outcomes is. To manage this, the study team can prioritise a speciality area of radiotherapy delivery and group of patients where, as much as possible, there is greater certainty in the relationship between dose and patient outcomes.

- If there is limited data or research evidence to inform model parameters, this will create a high degree of uncertainty in the model estimates. As an alternative to collecting data, the study team has the option more extensively consult or bring together experts and use deliberative techniques to reach a consensus on model assumptions.
- Timings to set the model parameters are tight and it is possible the study team will over-run on timings to review the research literature or analyse data. To mitigate this, the study should include multiple team members to lead on different aspects of desk research and analysis, and bring in researcher or academic expertise where this helps draw on, and make sense of, research evidence rapidly.
- It is possible that the model will simplify complex dose-response relationships and radiotherapy effects in the model. This can be mitigated through involving radiotherapy and oncology experts in the model development and validation. Some model simplification may be necessary in the short project timeframe and trade-offs should be explored with the experts.
- There may be delays in engaging and coordinating timely input from the range of experts and stakeholders needed. Outreach should take place at an early point in the study, draw on connections that NPL staff have with peers where possible, and set out a strong case for the benefits of participating in the work to inform government spending decisions.

4.1.6 Capabilities required

Given the nature of the project, it is critical to ensure that the project team includes or involves input from experts with expertise in the subject matter (radiation dosimetry), oncology, radiation biology, data analysis and economics. As part of this, is important that the core study team engages regularly with the radiation dosimetry team at the NPL. For the timescales of the CSR, this engagement will be especially important to adapt to emerging evidence and consider the most pragmatic approach to generating short-term evidence as opposed to conducting a longer-

term and more robust study. The multidisciplinary and multi-stakeholder nature of the work will require careful project management and coordinated from a dedicated study lead or project manager.

The core team will require an analyst, data scientist or modelling lead to lead on the analysis. There will ideally also be an additional team member providing quality assurance or oversight on the modelling approach. 1-2 additional NPL staff members or external researchers will also lead on conducting interviews with experts and reviewing research evidence in the literature.

To exact expertise the study team draws on will, in part, depend on the nature of the topic it prioritises. For instance, if the model focuses on a patient cohort receiving delivery of Stereotactic Ablative Radiotherapy (SABR) then expert conversations will need to take place with clinical specialists who are knowledgeable in the delivery of this service. It is advised that the NPL radiation dosimetry team provides introductions to relevant contacts across the network of NHS Trusts it works with to enable the most targeted conversations to take place.

In terms of researchers and organisations which can deliver the package of work, the overall modelling approach will require health economics expertise. The following research institutes regularly develop simulation models to assess healthcare interventions. For instance:

- The Health Economics and Decision Science (HEDS) group at the University of Sheffield's Centre for Health and Related Research (SCHaRR)
- The Centre for Health Economics (CHE) at the University of York
- The Health Economics Research Group (HERG) at Brunel University
- The Health Economics and Systems Analysis Group (HESA) at the London School of Hygiene & Tropical Medicine (LSHTM)

The fast nature of the work will however potentially mean that project delivery takes place instead with consulting firms with experience in health economics and modelling. Additional advice should also come from:

- the NPL radiation dosimetry team should play a close role in advising the project;
- additional modelling, statistics, or health economics professions to advise on the model selection, approach and communicating results;
- and clinical experts to validate model assumptions.

4.2 Radiopharmaceuticals – extending domestic sources of supply

4.2.1 Overview of approach and evidence generation

The UK market for radionuclides and radiopharmaceuticals consists of manufacturers for what are well-known and easily procured products (such as Fluorine-18). These manufacturers sit across companies, healthcare providers and in some cases universities.

The National Measurement System also conducts research to support the approval of new radiopharmaceuticals. The Nuclear Metrology team at the NMS is long-standing and has over time contributed to research which has accelerated the approval of radiopharmaceuticals which have applications to diagnosis and treatment methods. These include Thorium-227, Radium-223 and Terbium-155. The NPL works to develop new standards and data for new radioisotopes with medical applications, which supports regulatory approval with the Medicines and Healthcare products Regulatory Agency (MHRA) and other international medical device regulators. It does so as part of international collaborations such as PRISMAP which provides access to radioisotopes for research.

The Nuclear Metrology team provides primary standards of radioactivity for existing and novel radionuclides. It also provides measurement and calibration advice to sites using radionuclides, researchers developing new processes for the production of radionuclides, and manufacturers of radiopharmaceuticals. Ensuring that radiopharmaceuticals can be produced and delivered within measurement is necessary for their safe and effective use.

The UK has historically relied on a larger overseas supply chain for radionuclides and its supply chain is at risk from the closure of overseas production facilities such as research reactors and global supply shocks. More broadly, it is important that the UK develops its infrastructure for radionuclide production. This supports UK manufacturers and also improves resilience in the domestic supply chain. The UK government has initiated research and development activity focusing on developing domestic radionuclides production through the Medical Radionuclide Innovation Programme (MRIP), which is supporting 10 projects in total across academia and industry to research technologies and techniques that could strengthen the UK’s access to medical radionuclides. The NPL is leading two projects as part of this programme. This programme is underway and focuses on early research for radiopharmaceuticals. NPL is not solely responsible for producing medical radionuclides at the scale needed, however it is in a strong position to coordinate efforts to increase production. Given that the MRIP programme is at an early stage, there is no evidence of impact available for the project at this point in time.

NPL has, however, undertaken historic work to approve where new radionuclides and radiopharmaceuticals as medical products, including for UK based suppliers. For the purposes of the CSR, in which the UK government is the primary audience, it will be necessary to demonstrate that the approval of standards for new radionuclides or radiopharmaceuticals – where NPL has contributed to or accelerated regulatory approval – has led to a growth in the domestic market.

The aim of this proposed study is to assess how the research and generation of standards from NPL's Nuclear Metrology team are supporting the growth of UK manufacturers, potentially enabling new products and suppliers to enter the market, by analysing company growth and investment trends. This work sits across the **Collaborative Research** and **Commercial R&D** pathways within the Theory of Change.

Contribution claim

- **If…** NMS measurement scientists contribute to research and development activities that develop standards for near-to-market radionuclides or radiopharmaceuticals, along with new methods for domestic production
- **Then…** UK-based commercial manufacturers can adopt this research and development to increase domestic production of radionuclides and radiopharmaceuticals across a wider range of products.
- **This will lead to…** the introduction of new companies or research spin-offs as domestic manufacturers for radiopharmaceuticals, along with growth in the revenue, headcount and investment of existing manufacturers.
- **Ultimately…** growing the overall radiopharmaceuticals market, enhancing supply chain resilience and the potential for novel diagnostic and therapeutic products

The nature of benefits in this proposed study focus on historic commercial benefits data for UK-based manufacturers of radionuclides and radiopharmaceuticals. This may include the radiopharmaceuticals cited above or other known products on the UK market, which the NPL Nuclear Metrology team can advise on. Given reporting lags in commercial data sources, the focus of this study may necessarily be more historic approvals of radiopharmaceuticals (i.e., approvals that precede the previous CSR in 2021).

A comparison trend may be possible to draw out in terms of the potential delay in the approval and commercialisation of radiopharmaceuticals without the involvement of NPL, which in effect

would delay the ability of UK manufacturers to grow their business and potentially diminish the observed economic benefits. This comparison will be subject to assumptions made through expert input from NPL and other specialist staff and will not be an exact or experimental counterfactual to the NPL. It will not necessarily be possible to quantitatively separate out other effects on the market, as per a QED or RCT study, but through the contribution analysis approach it is possible to identify and develop an evidence base for which factors have had an effect on the market.

Event studies or econometric analysis, while possible in theory if applied to a set of companies, will not necessarily be possible on its own without carefully considering the size and type of company. For instance, this type of analysis will perform better where companies exclusively focus on the radiopharmaceuticals market, and at the very least radiopharmaceuticals must be a significant contributor to the company's overall growth. A contribution analysis approach is suggested as the primary framework to set out and test claims against evidence for this reason. Alternatively, the priority for this study may be to work closely with the Nuclear Metrology team to develop a specific case study where it is known that the NPL contribution has led to faster development and commercialisation of a product among domestic manufacturers.

4.2.2 Methodology

Through interviewing a specific set of companies and analysing investment trends we can report on historic growth in the sector and assess the extent to which this is due to research and standards set out by the NMS. The project will employ a mixed-methods approach, combining quantitative analysis of company and investment data with qualitative insights from industry experts and clinical professionals. This evidence will also help to test the study contribution claim. The study methods will include:

1. **Identification of sector and relevant companies:** Analysis of NPL held client data on companies or research institutes which manufacture and handle radiopharmaceuticals and radionuclides which the NMS has supported the approval of. A web-based scan for additional manufacturers will also help to identify other UK companies that may not directly interact with NPL but adopt its standards.

2. **Investment trend analysis:** The study team will use a financial analysis platform (see 4.2.3) to quickly gather and analyse data on revenue, headcount, and investment deals in UK-based radionuclides and radiopharmaceuticals manufacturers over the timeframe where the NMS has contributed to accelerating the approval of standards.

3. **Manufacturer interviews:** Semi-structured interviews will take place with key stakeholders, including representatives from UK-based manufacturers and NMS measurement scientists. These interviews will explore the degree to which company outcomes and growth are attributable to NMS involvement, research and standards, along with expectations on future growth. It will also seek to identify other factors which may have contributed to company growth.

4. **Analyse and summarise results:** The team will present the financial analysis together with interview findings and a revised claim drawing on the evidence sources in the above steps.

4.2.3 Data sources

This study will seek market data on UK-based manufacturers, including revenue and early investment, or grants from government programmes. To collect market data at pace, a financial analysis platform will be necessary. There are several on the market however three commonly used in evaluation studies by government bodies and research consultancies are set out in the table below:

Source	**Type of data**	**Key considerations and access requirements**
Manufacturers of radiopharmaceuticals or radionuclides which have engaged with the NPL Nuclear Metrology team	Companies names or identifiers	N/A
PitchBook	Financial analysis platform – these resources gather data on public and private companies online and from official sources. These allow researchers to search for	PitchBook does not publicly provide a set price however the price per annum is understood, on enquiry, to be upward of £20,000 per user. A minimum user requirement may apply.

<table>
<tr><td>FAME (Financial Analysis Made Easy)</td><td rowspan="2">company data using names and key search terms to extract:
Company revenue
Company headcount
Private investment
Access to each platform is relatively immediate, following on from any initial onboarding or training required.

The source of information such as revenue varies by platform. FAME provides comprehensive information on public and private companies. Coverage of companies in PitchBook and Beauhurst leans more towards public companies.</td><td>FAME provides pricing on the Gov.UK digital marketplace at around £6k per user (when arranging subscriptions for under five users). It is understood that FAME will allow single-user subscriptions for nonprofit organisations (link here)</td></tr>
<tr><td>Beauhurst</td><td>Beauhurst does not publicly provide a set price however the price per annum is understood, on enquiry, to range from £5k to £25k per user depending on the level of access needed.</td></tr>
</table>

For the shorter duration of the project and given the high costs associated with accessing annual subscriptions for the financial analysis platforms, it may also be a practical alternative to commission an external analyst to provide financial data on companies via PitchBook or another platform, however it will be necessary to check with a contractor what information they are able to share under their platform's license conditions.

An alternative data source not raised above is the ONS Business Structure Database. This is an annual extract of the Inter-department Business Register (IDBR), providing data on all organisations registered for VAT or that pay at least one member of staff through Pay As You Earn tax. It is one of the largest sources of data about business organisations in the UK. The ONS BSD contains information at a granular level on companies. However, accessing the ONS data is subject to reporting lags and requires ONS-accredited researchers, whereas access PitchBook or other platforms can happen immediately.

4.2.4 Indicative timeline

The timeline presented here is indicative, with a view that the study team will need to be pragmatic to generate evidence quickly, and adapt the approach based on the type of evidence arising.

In anticipation of the CSR, the study will need to generate and report headline findings over a short 3-to-4- month period. This will require fast gathering of evidence and analysis.

In **month one** the team should identify relevant companies to analyse. These will include UK-based companies in client-level data that the NPL holds which have developed or are developing radiopharmaceuticals.. Identification of companies and partners should heavily involve discussions with the Nuclear Metrology team in NPL to consider which organisations are most appropriate and for which commercial data is available.

In **month two** the team should execute a structured analysis of available time series financial data for these companies. This will include investment, revenue, and headcount. Companies may be at an early stage in growth, however investments and valuations in funding rounds will be a reflection of the market's expectations for future company growth and profitability.

Across **months two and three** interviews will take place to validate and interpret the financial data. This will query the contribution of NMS to those public and private organisations receiving investment and industry growth.

In **month four** the investment trends, corroborated by testimony of research standards adoption, will provide a narrative to support the argument that company growth has followed through – at least in part – due to the regulatory approval of a radiopharmaceutical product for which the NPL developed standards.

4.2.5 Key risks to manage

The study team will need to adapt to emerging evidence and consider what is practical and make the strongest argument at the CSR. This may include exploring alternative approaches, for instance working with Nuclear Metrology colleagues at NPL have also raised possible alternative case studies that can highlight examples from their historic work. The main study risks identified are as follows:

- Given that much of the work undertaken by the National Physical Laboratory focuses on international standards, and the domestic production capabilities of the UK are known to be limited, there is a high risk that the study finds that the NPL is not contributing to the

growth of the UK market and in fact is contributing to the growth of international production of radionuclides. If this is the case, the study team will need to switch their focus rapidly to consider how the work of NPL is contributing to measurable benefits within the UK. This may require the team to pivot to sharing case study examples of clinical trials outcomes – where the NPL has been involved – where the products in question are now implemented into clinical practice in NHS settings.

- The potential concentration of manufacturing activities away from companies in the radionuclides and radiopharmaceuticals sector may limit the scope of any investment trend analysis, which primarily would rely on company data. The same data will not be available in the same format for government laboratories or university facilities, for example. In addition, where companies do manufacture medical products, they may operate privately and only disclose limited information. Much of the research and development activity the UK government is funding appears to take place within research organisations and labs such as NPL and the National Nuclear Laboratory. If there are a small number of active companies, the study may wish to consider a more detailed account of the research activity within NPL or run a case study on a small number of specific companies it has supported.. There are a small number of companies which are participating in the MRIP programme for instance, and the study analysis could instead focus in on whether these companies benefit from the NPL as part of collaborative relationships between industry and government.
- The study relies on the willingness and availability of key stakeholders, including representatives from UK-based manufacturers, to participate in interviews. A low response rate or difficulty in securing interviews can impact on the quality and depth of the qualitative insights. To mitigate this, the study team should share interview invites from the study outset. The team should work through experts in the NPL Nuclear Metrology team to identify potential partners with close relationships to the lab, in order to improve response. The invite to interview should set out the value of contributing to the work, in terms of helping to inform government spending on NMS research and services.

4.2.6 Capabilities required

It is important that the core study team works pragmatically and iteratively with teams across the NMS in order to meet the timescale for CSR and adapt to emerging evidence. This requires careful project management and ownership from a study lead or team member within NPL or NML.

The project will require a dedicated team comprising a project lead and data analyst. The project lead will manage the overall study and lead on interviews and writing up project findings. The data analyst will need to have the license of credentials to access financial data via FAME, Beauhurst or PitchBook. This may mean that the data analyst is an external researcher with access to the data. The NPL Nuclear Metrology team should work closely with the project team to advise the work.

The study can involve both senior academics across UK universities who are conducting research into company performance, as well as consultancies. A brief search of academics for instance highlights Professor John Van Reenen of the London School of Economics, Jonathan Haskel of Imperial College's Business School who both research productivity and innovation across companies. Multiple consulting firms will be able to meet a specification covering the financial analysis of firms. For the purposes of analysing data, a freelance financial researcher or analyst may also be sought as part of a smaller contract.

4.3 Ultrasound screening for foetal anomalies

4.3.1 Overview of approach and evidence generation

Diagnostic ultrasound is the second most frequent imaging modality, with the number of ultrasound scans growing at a rate of 10 per cent year in England. Foetal scans form 20% of total images (2 million out of a total of 10 million) carried out in England. Diagnostic ultrasound also contributes to other major screening programmes including the NHS Breast Screening Programme and the National Abdominal Aortic Aneurysm Screening Programme.

NPL plays an important role in ensuring the safety and efficacy of diagnostic ultrasound by setting and maintaining standards for acoustic output, which is the amount of energy emitted by ultrasound scanners. It calibrates the hydrophones used by manufacturers to measure this output, ensuring that the devices operate within safe limits set by regulatory bodies like the US Food and Drug Administration (FDA) and the International Electrotechnical Commission (IEC). By providing calibration services with a low level of uncertainty in this output, NPL enables manufacturers to explore the use of higher ultrasound frequencies. This in turn can contribute to improved spatial resolution in diagnostic images.

Feedback from the NPL's ultrasound team indicates that NPL's uncertainties are lower, which means by using NPL's higher calibration frequencies, and lower output uncertainties, the manufacturers are more likely to have applied more energy to improve the image quality while still operating within the exposure limits.

Improvements in image resolution and accuracy should enable the early and precise detection of foetal conditions. Standards and measurement services, developed by NPL, support manufacturers of ultrasound devices and contribute to improvements in ultrasound technology. By providing more detailed foetal imaging, it is possible to improve the Detection Rate of structural abnormalities and other conditions during pregnancy. This provides important information for better-informed prenatal care and delivery and enables the arrangement of specialised care. This can reduce the time a neonate spends in neonatal intensive care and reduce potential complications at birth. Research which the NPL publishes are available to all device manufacturers. This means that it should be possible to see improvements in the rate of detection of foetal conditions across most or all ultrasound manufacturers, This does however mean it is not possible to identify whether there is a complete counterfactual group of companies which do not improve their product's image resolution using the NPL's services.

The current rate of detection for foetal conditions varies widely, depending on the condition and type of abnormality. The detection of Congenital Heart Disease (CHD) can vary considerably

depending on the complexity of the defect, the skill of the operator, and the equipment used. Prenatal detection of CHD can ensure the neonate receives prompt surgical intervention which may reduce their time in hospital, the severity of their condition and the cost to the healthcare system. Where this variation in detection remains, it emphasises the importance of supporting the reliability of ultrasound devices in detecting conditions.

NHS England (previously, Public Health England) carries out the NHS Foetal Anomaly Screening Programme (FASP) which screens for 11 conditions. Among the conditions, it is essential to prioritise those conditions where there has been the highest potential to improve detection and make meaningful changes to prenatal or postnatal care. Of the conditions, high potential study options include CHD and Spina Bifida, where improved detection rates can allow for prenatal surgery to offer better outcomes in terms of mobility for the child.

This proposed study will analyse trends in the Detection Rate of foetal anomalies, cross-reference this to testimony from manufacturers on improvements in ultrasound diagnostic technologies, and the potential contribution of measurement standards or services to these improvements. The study will also draw on research evidence and expert clinical input on the potential improvement to neonatal clinical outcomes and health system savings for the improvement in detection. This work considers the **Collaborative Research** and **Technical Consulting** pathways within the Theory of Change.

Contribution claim

- **If…** specialists working in the NMS have enabled ultrasound device manufacturers to use standards and measurement services in new devices for ultrasound devices for prenatal screening
- **Then…** this has allowed for the successful development and deployment of devices with greater reliability and accuracy to detect and visualise foetal conditions or abnormalities
- **This will lead to…** improved prenatal rates of detection for foetal conditions as part of NHS clinical screening programmes, with earlier and improved planning of specialist prenatal treatment, and surgery or treatment for neonates
- **Ultimately…** leading to better prepared clinical teams upon delivery who can support neonates, reducing the severity of any complications at birth, time spent in Neonatal

ICU and cost of providing urgent healthcare, while increasing the quality of life and development for newborns.

The nature of benefits in this proposed study can focus on historic information on improvements in ultrasound manufacturing, drawn from manufacturers which NPL interacts with, as well as historic information on the adoption of ultrasound devices into clinical practice and screening data held by NHS England or other NHS organisations. The contribution analysis approach can help to draw out evidence that supports the claim as a whole and strengthens the position of the claim in relation to other factors which may contribute to improved detection (for instance, wider changes to clinical pathways or practice).

4.3.2 Methodology

The study will employ a mixed-methods approach, combining quantitative analysis of screening data with qualitative insights from NMS staff, medical device manufacturers and clinicians, including operators of ultrasound equipment. The primary methods will include:

1. **Project planning and condition selection:** Across the 11 foetal anomalies NHS England tracks, the project team will undertake a structured prioritisation activity to focus one or a small sub-set of these. This will consider those with the greatest potential for improving the Detection Rate and those which clinical teams can act on. This decision may need to draw on a preliminary assessment of trends in the Detection Rates in the screening data (for instance, which conditions saw the greatest improvement in detection) and clinical expert input as a start point.

2. **Data analysis:** For the selected anomalies, the team will analyse NHS England's screening data over recent years to identify trends in detection rates. These trends may be due to improvements in screening technology however other changes in clinical practice or the running of FASP may also be relevant. Alongside the screening data, the team should review NMS held client data for ultrasound device manufacturers and cross-reference this to recent products or patents associated with these manufacturers. It is also valuable to consider whether an impact assessment or business case for FASP is available which also sets out economic analysis and assumptions which the study team can draw from.

3. **Interviews and expert consultation:** Separately, the study team will need to form a view on the adoption of devices into practice, and the contribution of these devices to an improvement in the detection rate for foetal conditions. This requires further investigation with the cooperation of device manufacturers (to understand where their devices are in

use) and NHS organisations or clinical settings. Interviews will take place with staff at the Department of Health and Social Care (DHSC) or NHS England involved in the FASP, clinicians involved in prenatal and neonatal treatment, ultrasound manufacturers and ultrasound operators. Discussions with these groups should provide qualitative insight and assumptions on improvements and health system savings as a result of improving the Detection Rate for the selected foetal conditions, as well as greater understanding of what modern ultrasound devices can achieve and what has enabled this. In the case that there has not been a noticeable improvement in the Detection Rate in recent years, the study team may wish to be pragmatic and switch the focus of the study to explore what future improvement is possible and what would be necessary to reach this.

4. **Document review of clinical evidence:** Benefits to neonates and the health system are unlikely to be visible through nationally held data or costing information. Therefore, any assumptions on patients' health benefits and health system savings will need to draw from research literature which identifies outcomes or healthcare costs. In time for the CSR it is not practical for the team to undertake a full systematic review of the literature, however they can seek immediate evidence available on the potential health benefits of screening and early intervention for the condition(s) the study team has prioritised. As above, drawing on any pre-existing impact assessment or business case and FASP can also provide a quick source of evidence and assumptions.

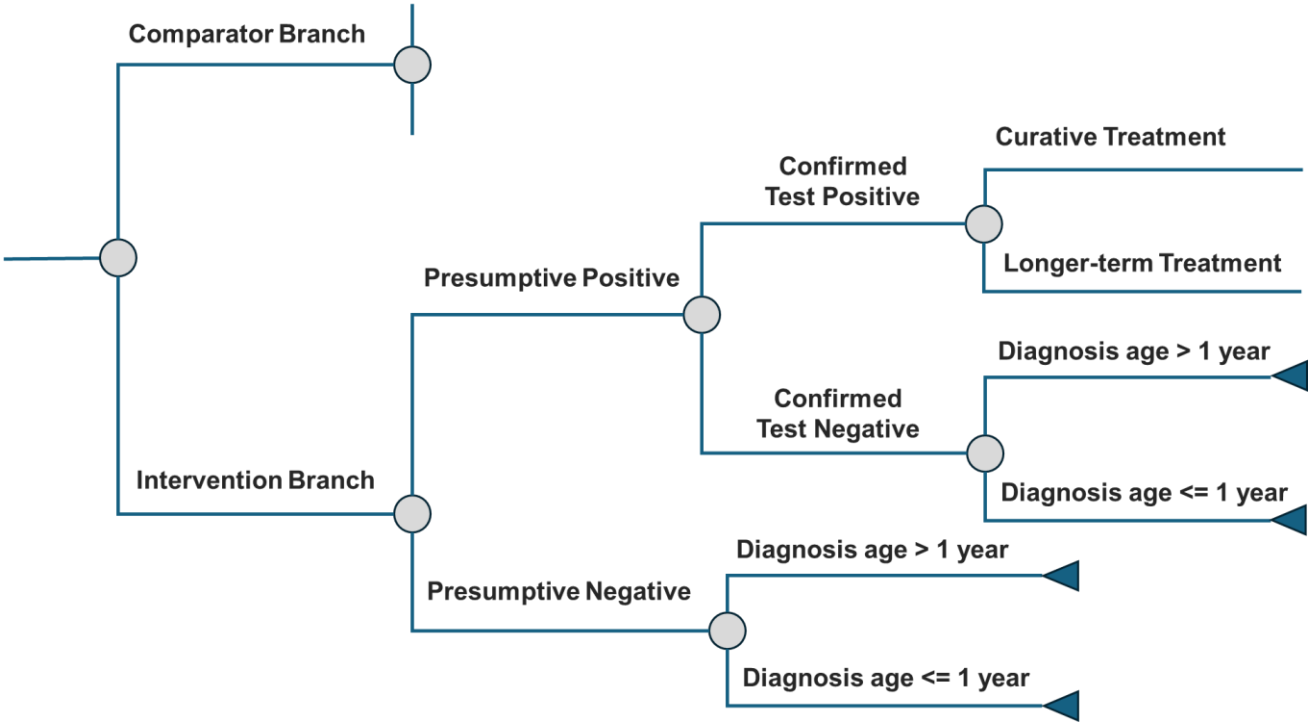
5. **Modelling patient benefits (if feasible):** If data on improvements in the Detection Rate of conditions show a clear improvement, and interviews and research evidence provide a clear testimony or assumptions for the NMS contribution of these improvements to patient or health system benefits, then it may be possible to design a model that approaches a decision problem for the chosen speciality area. As with the suggestions for a modelling approach in 4.1 the model and its key parameters will depend on the decision-problem under consideration. In this instance, the decision-problem relates to accuracy with which ultrasound equipment can detect foetal anomalies at set intervals during pregnancy. This is based on improvements in the accuracy of the screening programme which manufacturers can attribute to the adoption of standards or measurement services. In terms of set intervals, pregnant women are likely to receive a set number of scans at stages during pregnancy. For instance, a 'dating scan' that predicts the baby's due date and checks for certain syndromes and a second scan, between 18 to 21 weeks, to identify physical abnormalities in the baby. The key considerations are:

Model Structure: In this instance *decision tree* and *Markov health states transition* models are common model structures. As the screening processes happens over a small number of discrete times, the use of a simple decision tree can be suitable and practical where branches for each use of ultrasound splits patient outcomes by positive- and negative-detection of conditions. The probabilities that a diagnosis is accurate can feature along each branch, with assumptions around patient benefits or quality of life (taken from step 4 above) at the end of each branch. By using probabilities for correct or incorrect detection of conditions, a decision tree model can set out the degree to which patient benefits arise with a change in probability – for instance, from improvements in the probability that a patient is screened as a 'true positive' for their condition due to improvements in ultrasound measurement. A decision model can typically be set out in TreeAge, Excel, R or Python and is a simpler start point for the purposes of generating a quick model for the CSR.

A Markov model is valuable for dealing with situations where the patient's health state changes over time. For instance, it would allow a modeller to capture any difference in how long the patient spent in different health states due to an earlier or later detection of a condition. It is also possible to combine the decision tree and Markov model approaches. For instance, the decision-tree can set out the screening pathway, with each branch leading to positive or negative detection of the condition. At the end of each branch, the neonate can then experience a different set of probabilities for moving between health states as part of the Markov model.

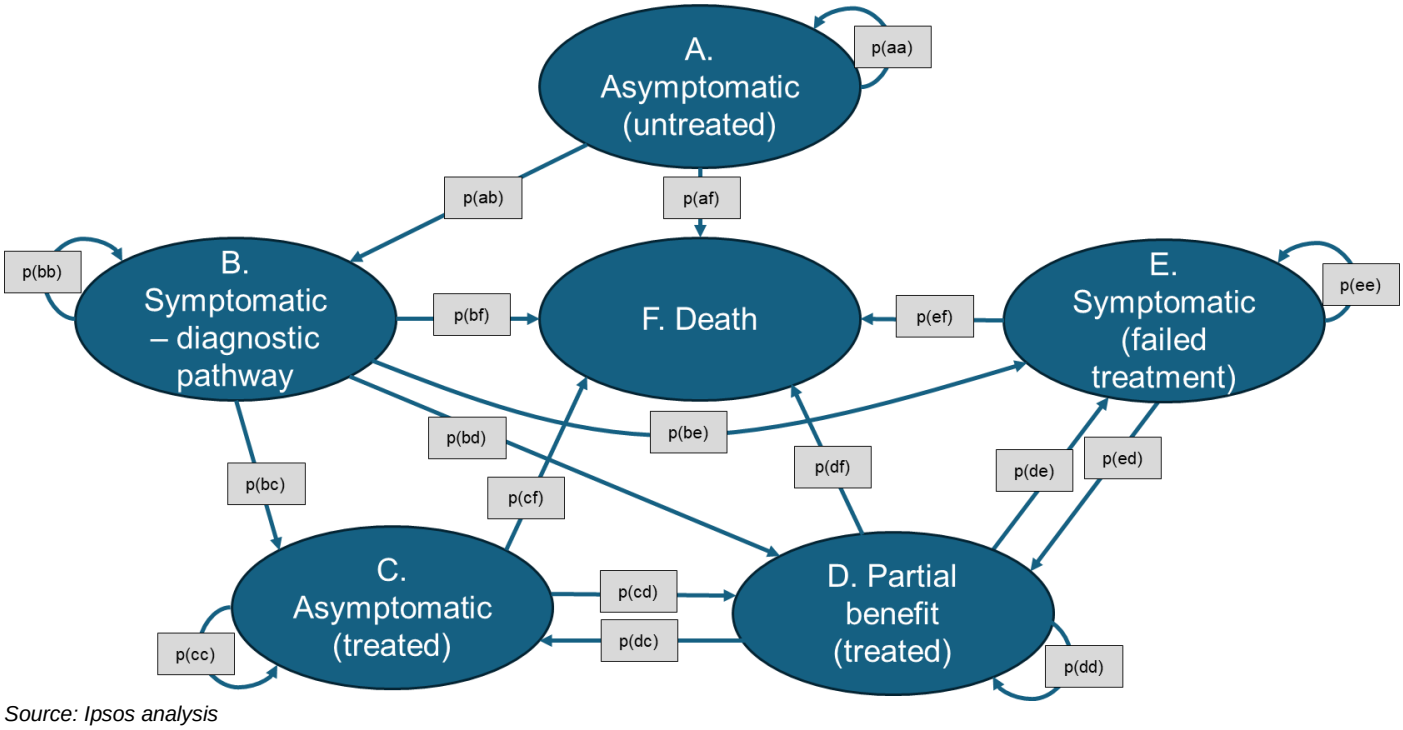
Depending on chosen structure, the study team will need to consider more detailed factors when setting up the model. For instance, which branches are necessary in the decision tree model to accurately represent the foetal screening pathway. Or, for the Markov approach, what the appropriate health states are which need capturing, over what timeframe after delivery, and how to estimate the probabilities for moving between health states. Figures 4.2 and 4.3 below are illustrative examples of the two modelling approaches in a similar screening use case.

Figure 4.2: Example illustrative *decision tree model* structure for a screening use case – the initial branch represents a split in the intervention and comparator treatment (e.g., high vs low precision calibration) with subsequent branches representing aspects within the patient pathway.



Source: Ipsos analysis

Figure 4.3: Example illustrative *Markov transition model* structure for a screening use case – each oval represents a health state that the patient or cohort of patients enter at a discrete point in time. These will each have an associated quality of life from full health / high quality of life to low quality of life and death. There is a probability (transition probability) assigned to the likelihood that a patient moves from one state to the other based on their course of treatment. These probabilities may be varied according to the precision / effectiveness of the course of treatment received.



Source: Ipsos analysis

Comparators: There is not a clear comparator to include in the model as most manufacturers will be able to access standards and services the NMS provides, and a true QED approach is not possible to consider for the reasons set out in section 2. Therefore, any modelling will need to draw heavily on feedback on manufacturers on the degree to which their products have improved in recent years and on what grounds.

*Identifying patient benefits***:** The specific nature of benefits will vary by condition but can broadly be considered using Quality Adjusted Life Year (QALY) improvements in early years of life alongside health system financial benefits, depending on the types of benefits healthcare staff raise in interviews or that are visible in document reviews. As a national screening programme, FASP may also have conducted a previous impact assessment for the programme. It will be relevant for the study team to request any prior work that DHSC or NHS England may be able to provide to support the study.

There are multiple instances where researchers have applied health economic modelling to screening use cases. A small number of illustrative examples are set out in **Appendix 2**.

6. **Synthesis and reporting:** For the purposes of the CSR, initial reporting will focus on headline patient or health system benefits and the contribution NMS has made to these, along with testimony from interviewees. Further reporting and dissemination will be possible following on from this.

4.3.3 Data sources

The nature of this study. in exploring upstream contributions from the NPL to device manufacturers, and downstream effects on healthcare delivery, will mean that a variety of NPL, academic and publicly published data sources will need considering and bringing together. The NPL holds data on the device manufacturers it works closely with, while the UK government publishes publicly available annual reports on Gov.uk setting out the Detection Rates for foetal conditions, in terms of the number of cases detected relative to those expected or diagnosed postnatally.

Source	**Type of data**	**Key considerations and access requirements**
Device manufacturers affiliated with NPL	Company names or identifiers	N/A

Ultrasound measurement services		
PubMed, Cochrane Library, ClinicalTrials.gov	Research portals which provides access to a database of citations and abstracts across medical fields to enable review of literature for potential assumptions, as part of literature review approaches	Full texts of articles may require a subscription or purchase from the publisher; however, some articles will be available through PubMed Central. It should be considered that the team conducting the work budgets for or can access articles
FASP Screening Standards	DHSC regularly publishes screening standards that outline the quality and performance for providers of foetal ultrasound screening. These set out, for instance, the rate of detection achieved in clinical practice. This can set out the range in detections for conditions over the last 5-6 years to reconcile with testimony from device manufacturers	Open to access online at gov.uk

Further data and assumptions (such as quality of life or lifespan benefits, or health system savings) will need to draw on research literature using online databases and a search strategy. Discussion with DHSC and NHS England will also help to draw out whether there are any prior data and assumptions used for impact assessments and business cases for the FASP itself.

4.3.4 Indicative timeline

The timeline presented here is indicative, with a view that the study team will need to be pragmatic to generate evidence quickly, and adapt the approach based on the type of evidence arising.

In anticipation of the CSR, the study will need to generate and report headline findings over a short 3-to-4- month period. This will require fast gathering of evidence and analysis. For this project in particular, this fast turnaround will be challenging and requires careful prioritisation of which conditions are in-scope for the study and how much time to commit across: analysis of screening data, analysis of wider company data, document review and interviews. The approach will need to be pragmatic, and the project team will need to revisit what approach and balance of evidence is most suitable. Further extension of the scope of the work may be desirable following on from the CSR period. It is unlikely, within 3-4 months, that a full chain of effect from measurement service to device manufacture to clinical adoption and outcomes will be possible to evidence. However, aspects of this pathway - as set out in the contribution claim – can be gathered and triangulated to support the claim.

In **month one** the team should plan and assign staff to the analysis, document review and interviews workstreams and set a clear scope for the conditions it reviews. The team should also shortlist and invite interviewees to discussion.

In **month two** the team should analyse trends in the Detection Rate for its chosen conditions, identify the total population diagnosed with the condition, review associated literature on the benefits of early detection of these conditions and begin interviews.

In **month three**, any final interviews should take place. The team should come together to assess findings from the data analysis, document review and interview findings to assess the best approach to reconcile these findings and develop a narrative. This may include revisiting the project contribution claim. If a quick top-down modelling approach is possible that can put an indicative figure on population-wide benefits as a result of improvements in Ultrasound Detection, this should happen quickly and pragmatically over this month. This will likely generate an initial version of the model with a headline figure to use, with further opportunities to develop this in full following the CSR.

In **month four** the findings, either as a narrative and / or headline modelling output, should be written up and presented. Some final discussion with NHS England or clinical staff may be necessary to help validate the study findings.

In later months, the team may wish to revisit and refine the approach it took, including extending the project scope, modelling approach or treatments considered.

4.3.5 Key risks to manage

The main study risks identified are as follows:

- The team may encounter challenging or inconclusive findings on whether there have been improvements in ultrasound detection or around patient and health system benefits. For instance, it is possible that FASP screening data does not show an adequate trend in Detection Rate improvements in recent years. Available research evidence on the benefits associated with improved prenatal detection may be limited or present highly uncertain ranges. It may, also, be difficult to separate out the contribution of prenatal treatment from other clinical practice when considering patient outcomes.

  To account for this, it will be necessary to engage with NHS England and the screening programme at an early stage in the study to secure access to any additional data, assumptions and subject expertise and explore how to approach these limitations. Any prior or related work by NHS England may help to inform the project at an early stage. Greater time may also need to focus on interviews and consultation with manufacturers and clinical experts. If there are not historic improvements in Detection Rates in recent years of the FASP, the analysis may want to re-focus on future years rather than historic data and focus on what the potential for improved detection is in future.

- The study timings are short and there are multiple fieldwork workstreams covering external interviews with stakeholders, analysis of data and document review. The study team must meet and assess timings regularly, prioritise early outreach to stakeholders from the outset of the project, and regularly assess the approach to the study if there are delays to timings or unexpected challenges arise.

4.3.6 Capabilities required

It is important that the core study team works pragmatically and iteratively with teams across the NMS in order to meet the timescale for CSR and adapt to emerging evidence. This requires careful project management and ownership from a study lead or team member within NPL or NML, and close involvement of the NPL ultrasound team.

As with the example in 4.1, involving researchers which are familiar with analysis and health economic modelling can be beneficial when considering the potential health outcomes and cost savings that would arise as a result of improved screening. As before, researchers across the University of Sheffield's Centre for Health and Related Research (SCHaRR), Centre for Health Economics (CHE) at the University of York, The Health Economics Research Group (HERG) at Brunel University and The Health Economics and Systems Analysis Group (HESA) at the London School of Hygiene & Tropical Medicine (LSHTM) would, as a small set of examples, have faculties which can provide this work, especially when considering modelling and literature

review approaches. The additional engagement with device manufacturers may benefit, specifically, for additional qualitative researcher or consultancy support where experience is necessary to conduct structured interviews that serve to better understand improvements in ultrasound screening.

The study will require a dedicated team comprising a 1-2 lead researchers and a data analyst, to conduct data analysis, document review and interview work between them. The research into the benefits of early detection of foetal conditions may benefit from the involvement of an external clinical researcher. It may also be valuable to include an external researcher to quality assure or advise on any modelling approach undertaken. It will be essential for both clinical specialists and the NPL ultrasound team to advise the study regularly as it progresses.

4.4 Established nanomedicines in clinical practice

4.4.1 Overview of approach and evidence generation

NMS work on nanotechnology seeks to quantify materials at the nanometre scale. There are variety of healthcare applications for these materials.

Both the NPL and NML research nanotechnology with healthcare applications. Each focuses on the measurement accuracy of these technologies and their interaction with biological systems. The development of clear measurement standards and techniques is necessary to ensure the safety and efficacy of any nanotechnology products used in clinical settings, and to ensure reproducibility and comparability of the technologies across labs and real-world settings. From a measurement perspective, this includes through more accurately quantifying and characterising nanoparticles and nanomaterials, considering their suitability for use in diagnostic and therapeutic applications, and monitoring how nanoparticles behave in biological environments. Within this field of research, nanomedicines are sub-field of nanotechnology and cover medical applications of nanotechnology for diagnosis, prevention, and treatment. Nanotherapeutics are a further subset of this. The maturity of nanotechnology in healthcare ranges from well-established treatments which are integrated into clinical pathways through to early-stage technologies.

In the former case of nanomedicines, small and medium-sized enterprises (SMEs) have adopted NMS standards and commercialised their technologies. There is a strong presence of nanotechnology companies in the UK with some wide-ranging examples including Oxford Nanopore Technologies, Sphere Fluidics and Endomag. Successful SMEs and research spinouts are often acquired into larger pharmaceutical companies. For instance, in the USA, Luminex acquired Nanosphere in 2016 and Pfizer acquired BIND Therapeutics the same year. It is important to also consider companies that manufacture instruments alongside the nanotechnology itself, such as Oxford Nanopore. NPL and NML hold data on both types of companies – medical devices and instrument manufacturers – as both are key stakeholders which benefit from NMS research.

This study will seek to define a group of UK-based nanotechnology manufacturers which have developed established nanotechnology products and instruments, measure trends in growth, investments, patents, regulatory approvals, and company acquisitions. Alongside this, interviews will seek to understand drivers in UK company growth and how NMS standards and research have contributed to each company's research and development. This work sits across the **Collaborative Research** and **Commercial R&D** pathways within the Theory of Change.

Contribution claim

- **If…** specialists in the NMS provide standards for manufacturers of nanotechnology devices and instruments, which allow for validating and standardising the production of nanomedicines
- **Then…** the successful implementation of measurement services and standards will provide a strong foundation for UK-based SMEs to develop, approve and commercialise nanotechnology products
- **This will lead to…** an increase in the growth of UK-based nanotechnology manufacturers, increasing their value, revenue, staff size and investment
- **Ultimately…** increasing the size and of the overall nanotechnology sector in healthcare, and increasing the number and range of products available to patients

The nature of benefits in this proposed study focus on historic commercial benefits data for UK manufacturers of nanotechnology products and instruments with a health and life sciences application. A comparison trend could be drawn out in terms of potential delays in the approval and commercialisation of nanotechnologies, which in effect would delay the ability of UK manufacturers to grow their business and potentially diminish the observed economic benefits. This comparison will be subject to assumptions made through expert input from NPL, NML and other specialist staff and would not be an exact or experimental counterfactual. It will not necessarily be possible to quantitatively separate out other effects on the market, however through the proposed contribution analysis approach it should be possible to identify other potential factors which have an effect on the market. In this case, the Contribution Analysis approach will need to consider the evidence for the above claim to hold true with respect to other potential factors which contribute to growth of the nanotechnology sector including other government initiatives, incentives from other international markets to set up business abroad and confidence of the investment market.

As with section 4.2, while event studies or econometric analysis of companies are possible in theory. In practice this will depend on the size and type of company in focus. For instance, whether the company focuses exclusively on nanotechnology, or at the very least this forms a large part of its commercial growth.

4.4.2 Methodology

The project will employ a mixed-methods approach, combining qualitative feedback from international partners and nanotechnology manufacturers with a financial analysis of companies. The primary methods will include:

1. **Define nanotechnology treatments or companies in scope:** Consultation with NMS experts and review of industry will take place to agree manufacturers and treatments in scope for analysis. This should include a review on client data NPL and NML held, and companies that NMS researchers have engaged with.

2. **Analysis of company and investment data:** Using a financial analysis platform, data on the UK-based manufacturers in scope in step 1 above will be collected and analysed to assess the commercial growth of each over the last ten years. This analysis will include metrics such as revenue, investments, employment, patents, and acquisitions.

3. **Qualitative feedback:** Semi-structured interviews or surveys will be conducted with relevant leads at nanotechnology companies (Chief Executive Officers, Chief Scientific Officers, R&D Leads) to understand what role and contribution NMS activities, research and standards have made to company research and development. Either data collection method will be structured to consider company adoption of standards alongside other factors that may have contributed to their growth.

4. **Reporting:** The financial analysis and qualitative feedback will come together with a revised contribution claim. For the CSR, the study team will present a headline growth figure for company along with a revised contribution claim and testimony from companies.

4.4.3 Data sources

For the financial analysis, it will be important to use a financial platforms such as PitchBook or an alternative. As previously set out in section 4.2.3 there are a variety of financial platforms and the pricing and licensing across these varies. There is also a separate option to hire an external researcher with access to financial data for the duration of the project, instead of paying for an annual product license.

Source	Type of data	Key considerations and access requirements
PitchBook	Financial analysis platform – these resources gather data on public and private companies online and from official sources. These allow researchers to search for company data using names and key search terms to extract: • Company revenue • Company headcount • Private investment Access to each platform is relatively immediate, following on from any initial onboarding or training required. The source of information such as revenue varies by platform. FAME provides comprehensive information on public and private companies. Coverage of companies in PitchBook and Beauhurst leans more towards public companies.	PitchBook does not publicly provide a set price however the price per annum is understood, on enquiry, to be upward of £20,000 per user. A minimum user requirement may apply.
FAME (Financial Analysis Made Easy)		FAME provides pricing on the Gov.UK digital marketplace at around £6k per user (when arranging subscriptions for under five users). It is understood that FAME will allow single-user subscriptions for nonprofit organisations (available here).
Beauhurst		Beauhurst does not publicly provide a set price however the price per annum is understood, on enquiry, to range from £5k to £25k per user depending on the level of access needed.

4.4.4 Indicative timeline

The timeline presented here is indicative, with a view that the study team will need to be pragmatic to generate evidence quickly, and adapt the approach based on the type of evidence arising.

In anticipation of the CSR, the study will need to generate and report headline findings onwards over a short 3-to-4- month period. This will require fast gathering of evidence and analysis.

In **month one** the team should work closely with nanotechnology specialists across the NMS to define the technologies and companies for which there is most likely to be a contribution from NMS research and standards, and where there is the greatest potential to observe commercial growth. Using client-level data held by NPL and NML and through additional scanning for companies (though drawing on an additional research partner, undertaking an online review of companies or a web crawling approach) the team will generate a sample list of companies to analyse. An outreach plan to Chief Scientific Officers or R&D directors at a sub-set of these companies should take place, either in the form of a small number of focused interviews, or via a proforma to collect information from a wider set of companies.

In **month two** the team should analyse trends in commercial growth going back over a 5–10 year time period. Due to the commercial nature of the sector, this will likely use a financial platform (such as PitchBook or alternatives raised in 4.4.3) to capture investment, acquisitions, revenue and staff headcount. As the nature of NMS research into nanotechnology is wide-ranging, the analysis will need to take place with expert input from NPL and NML regarding the timescales over which NMS research has contributed to the sector. This can then overlay onto trends in company growth that the study team identify.

Over **month two and three**, interviews or proforma data collection will take place. The priority of this activity will be to understand contributing factors to nanotechnology development and in what ways the company interacted with or used standards that were traceable to the NMS. In **month four**, write-up and dissemination of headline sector growth statistics will take place.

4.4.5 Key risks to manage

Risks for the project are as follows:

- There may be methodological challenges in securing commercial data on companies. Some privately held companies may not disclose their data. For any larger companies, which develop and commercialise a wider range of products that extend beyond healthcare-specific nanotechnology, it may not be possible to separate out what is

contributing to their financial reporting or performance. It is therefore likely that the analysis of data and trends will need to account for an incomplete dataset. To mitigate this the study team will need to respond practically and use interviews and surveys to fill gaps or provide additional qualitative information or case study accounts on companies.

- Companies may not be easily contactable at short notice, especially for interviews. Sharing a short survey or proforma with a short time commitment may be preferable to improve the response rate. Additionally, the study team may benefit from engaging with companies with a closer affiliation to staff working for NPL and NML. Setting out a clear benefits case for goals of the work, in terms of influencing governing spending, will also help to improve the response from interviewees.
- There may be some problems in gathering comprehensive sector data across a large number of nanotechnology companies. If this is the case, then an alternative approach would be to focus in on a specific company case study where the study team has available data, and where the company in question can provide detailed feedback on its relationship with NMS standards and services.

4.4.6 Capabilities required

It is important that the core study team works pragmatically and iteratively with teams across the NMS in order to meet the timescale for CSR and adapt to emerging evidence. This requires careful project management and ownership from a study lead or team member within NPL or NML.

The same skills and pre-requisites apply as in the study set out in 4.2. Academics across UK universities who are conducting research into company performance will be well-suited for the study, as will consultancies with experience in analysing company investment and growth trends. For the purposes of analysing data, a freelance financial researcher or analyst may also be sought as part of a smaller contract.

The project will require a dedicated team comprising a project lead and data analyst. The data analyst may be a member of NMS staff or an external researcher who has access to financial data. The involvement of NMS staff specialising in nanotechnology will be essential to guide the study, validate findings, provide subject expertise and advise on how to gather insight from companies the study team interview.

5 Long-term study plans

5.1 UK influence in international standards setting

The NMS plays a vital role in influencing international standards across several measurement science areas. A current example where this is taking place is in informing standards for novel nanotherapeutics such as targeted drug delivery agents. NMS staff represent MHRA and DSIT in international standards discussions. As part of this, the staff also engage with and represent the point of view of UK businesses. This considers the medical products UK businesses are developing and seeking to approve through UK and international regulators, to commercialise their products in the UK and abroad. The NMS will engage with partner organisations seeking its services as well as trade bodies.

A longer-term study can provide a detailed qualitative case study of how NMS staff go about informing international standards in a high priority case study topic. Based on discussions at options appraisal, standards for nanotherapeutics will be current and align with activities that both NPL and NML are undertaking. The study will seek to clarify in detail how the UK industry perspective is incorporated into developing standards and evaluate the nature and outcomes of conversations between UK measurement experts and bodies such as the International organization for Standardization (ISO).

The study will employ a qualitative case study approach, focusing on the testimony of NMS staff involved in international standards setting for novel nanotherapeutics. Semi-structured interviews will be conducted with NMS staff representing roles with MHRA and other relevant organisations, as well as stakeholders from DSIT, MHRA, trade bodies, and companies that work with the NMS. Relevant documents, such as meeting minutes, position papers, and draft standards, will be available to the study to team to review, to triangulate discussion from the interviews and understand the context around decisions undertaken. Preliminary findings will be shared with project stakeholders for validation and to gather additional insights on the potential benefits and impact of the standards on their businesses. Where ISO or other bodies' international standards are approved, a follow-up discussion should take place with industry stakeholders to take their feedback on the process and understand how this will affect their business operations. Ideally, follow-up discussion will be structured and ask specific questions around the commercial benefits to companies.

The qualitative research undertaken as part of the study will need to follow a couple of principles to remain robust. For instance, it will need to:

- Set out a clear research framework of the expected impact the NMS is having in influencing standards, and the potential loss of impact if NMS is not able to represent the UK in presenting its position. All questions and interviews should tie back to this research framework to test and confirm this.
- Sampling of interviewees will need to ensure representation from all relevant stakeholder groups in the UK and as part of international standards bodies which adopt or take on board advice from the NMS.
- Carry out a structured analysis of qualitative data using a coding framework that ties back to the study research framework. The coding will allow researchers to categorise common themes across each interviews focusing on value and impact from the NMS contribution.
- Conduct expert quality assurance on the approach, both from an experienced qualitative researcher and subject matter expects to adjust the study design as necessary.

Study timings, fieldwork and milestones can map across to key standards discussions taking place over a year. Early study planning will focus on scheduling and planning out stakeholder interviews around key standards discussions and decisions taking place.

The study requires a team lead and qualitative researcher, with potential additional costs for transcription. The study outcome will be a detailed qualitative account describing the NMS's role in shaping international standards and the expected positive impact for UK sector. The nature of the work in monitoring key meetings and processes may also present the opportunity to develop a process map of the NMS engagements with stakeholders.

5.2 Process mapping molecular diagnostics standards and regulatory processes

The COVID-19 pandemic has led to major changes in the development and deployment of diagnostic products in clinical pathways, at the point of care, and in the community over the last four years. Novel molecular diagnostics developed for COVID are also now being repurposed for additional clinical use cases and conditions. The NMS – in particular NML – has, in response to this, introduced regulation and measurement standards to support the development, validation, and deployment of COVID-19 molecular diagnostics in the UK. The development of this infrastructure has taken time to implement and in many respects progress is still underway to apply it to the regulation of novel diagnostics. It does, however, represent progress compared to what was in place prior to the COVID-19 pandemic. It already provides, for instance, a more structured approach to monitoring and assessing the accuracy of diagnostics, including through post-market surveillance, which was not previously in place.

A proposed longer-term project will research, map out and describe the current processes in place resulting from NMS activity around molecular diagnostics, in comparison to pre-COVID processes in place. This will seek to describe what potential impact these processes will have in terms of improved accuracy and reliability of diagnostics across various disease areas. Recognising that there is potential for future progress to develop regulations for diagnostics, the study will also consider 'how far along' current activities are and consider what future improvements in accuracy testing and surveillance may look like across various diagnostics use cases.

To achieve this, the study team will employ a qualitative, process-based approach. Given the nature of potential NMS impacts, we suggest using a process tracing approach, which will allow testing specific hypotheses on NMS impacts within a case-based setting of COVID-19 molecular diagnostic. This involves specifying formal tests (if X is found we consider this definite proof of NMS impact, etc) and then testing evidence against these tests. Evidence will include current materials detailing regulatory processes and standards, documents from the NMS at the point in time where new standards were introduced, conduct semi-structured interviews with key stakeholders, and explore case studies of specific COVID-19 molecular diagnostic which have run through the improved regulatory processes. The focus on data in this study will be mostly qualitative and process-based, with the study team drawing on quantitative or diagnostic performance data where it is available.

The findings of this assessment will provide valuable lessons learned following on from the COVID-19 response which can re-apply into other contexts to strengthen the UK's diagnostic capabilities and pandemic preparedness.

The project will take place over a longer timeframe and can run up to 12 months depending on the degree of thoroughness the team wish to take in reviewing and mapping out the standards and regulatory processes in place, as well as the degree to which they wish to explore potential future processes and case studies. The project will require a dedicated team comprising a project lead, 1-2 qualitative researchers. NMS staff specialising in molecular diagnostics and wider experts in regulatory processes should also advise and steer the project.

The findings for the study will be relevant to a variety of stakeholders including DSIT, DHSC, MHRA, researchers at NMS and partner bodies and trade bodies such as the British In Vitro Diagnostics Association (BIVDA). There is a broader potential for the work to inform future strategies and investments for the UK's diagnostic and MedTech industry while also demonstrating value in improving the standard of diagnostics for future CSR or business case rounds.

Appendix 1 – Longlist of topics not prioritised as part of scoping

Throughout the scoping process, Ipsos considered a range of topics in which the impact of the NMS could be measured. The options discussed in this paper were based upon feedback from consultations so that there was the greatest ability to identify impacts and test assumptions and balance across NPL and NML activities.

In January 2024, the Ipsos scoping study team met with scientific teams across NPL and NML. These discussions covered several topics and use cases where with potential public or economic benefits to measure. To practically proceed to develop study plans, it has, however been necessary to prioritise 'hot spots' where the ability to define impact and demonstrate causal assumptions are more possible.

Topics were de-prioritised as part consultation with NPL and NML staff at milestone workshops to ensure there was consensus in the direction of the scoping exercise.

As part of an interim project workshop in February, the Ipsos team proposed a shortlist of topics to consider for discussion along with an annexed list of additional topics. NPL and NML provided feedback on which topics across the shortlist and annex to take forward.

The topics agreed for further exploration at the workshop were: radiotherapy (radiation dosimetry), radiopharmaceuticals, ultrasound, nanotherapeutics, molecular diagnostics and data science. At the session, the group decided on the following **topics** to de-prioritise:

1. **Measurement techniques for chemical and biological environmental pollutants.** (air, water, microplastics, food). At an interim findings workshop this topic was de-prioritised as it was not a priority for the labs as part of this exercise.

2. **Measurement of genetic engineering techniques to support development of advanced therapies such as gene therapies for rare disease.** This topic area, while promising in future for NPL and NML, it was de-prioritised due to there not being as well-established an evidence base at present.

3. **Bioeconomy and bioengineering research for developing new tissues, medical devices, medicines, and materials for manufacturing.** While this is an emerging area of policy interest with a number of potential high-profile applications, the topic was de-

prioritised due to the earlier stage nature of the work and long timescale over which benefits would need to be considered.

4. **Measurement of pharmaceuticals and biological materials to analyse performance in developing new drugs e.g., antibiotics.** The scoping study team initially considered this topic area, given the high interest from government and industry in contributing to drug discovery and medicines manufacturing projects. However, due to the long-lead times and uncertainties in developing drugs, and the particularly busy nature of topics such as Antimicrobial Resistance, the team agreed to add the topic to a longlist.

Following this, an options workshop took place in March to consider in greater detail what study questions, data sources and methods would be preferable to prioritise within each topic area. Following conversations at this workshop with NPL and NML on each of the topics, the group agreed the following **focus areas for studies** to de-prioritise:

5. **Studies exploring the downstream commercial benefits of NPL radiotherapy research.** On discussion, it was agreed that a study focusing on radiotherapy instrument manufacturers would not have been useful for the CSR as most manufacturers operate outside the UK, with companies such as Varian, Elekta, Accuray and Siemens based across the United States and Europe. For the CSR, it is necessary to focus on growth in companies which are UK-based.

6. **Studies exploring clinical trials and clinical benefits of radiopharmaceuticals, as opposed to commercial benefits.** Through approval and implementation into clinical practice, a study would highlight the benefit to patients estimated. This would likely be a very narrowly focused case study that could not generalise across to a wider group of patients and for this reason we have not explored it further.

7. **Studies exploring the benefits from introducing novel ultrasound therapeutics applications to treat cancer.** Following workshop discussions with NPL and NML the Ipsos scoping study team instead focused on prioritising an ultrasound screening use case as opposed to a therapeutic use case rather than attempting to develop a study around both topic areas.

8. **Studies focusing on safety in the delivery of ultrasound doses to patients.** We could have also focused on a study that considered improvements in the safety aspects of ultrasound, from ensuring the right frequency is set. Following discussions with the NPL Ultrasound team we learned that the same calibration practices do not happen on a

regular basis for ultrasound as they do for radiotherapy. Given this, it would prove more difficult to draw on regular or 'live' data on calibrations – or on incidents where calibration is poorer – as the main contribution of measurement services is with manufacturers one-off at an earlier stage in the process.

9. **Measurement of nanotherapeutics for treatments e.g., cancer treatment.** The scoping study team agreed to consider nanotherapeutics as a topic area given its relevance to both NPL and NML. Nanotherapeutics, and more broadly nanotechnology, have wide-ranging applications to healthcare including drug delivery, surgery, and treatment. One promising application of nanotherapeutics is the targeted delivery of medicines in cancer patients. Following an options workshop, the focus on clinical and patient benefits aspects for this topic was de-prioritised due to the earlier stage nature of much work, long timescale over which benefits would need to be considered.

10. **NPL Data Science projects.** As part of the options appraisal workshop, we presented a potential study option on the NPL Data Science team's work with a partner NHS Trust to better monitor and present the performance of its clinical pathways. This study could have functioned as a case study review using a mix of qualitative and quantitative evidence. Upon consultation with NPL, it was decided that this activity was not connected clearly enough to the lab's measurement science work. We therefore did not pursue this topic further.

Appendix 2 – Illustrative examples of health economic modelling studies

Please note that the following are illustrative examples based on a brief scan which can be informative or use a method similar to the ones explored above. The exact source of data and assumptions for these models, and the exact choice of structure of the models, will differ from the approach that the NPL and NML would take for the specific use cases and decision problems they are exploring. It is also important to reiterate that the time to completion for the below studies is likely to exceed the 3-4 months necessary for NPL and NML to work towards for the CSR. These studies nevertheless provide an indication of the potential overall approach that NPL, NML or a research team on their behalf choose to take:

Examples of health economic modelling approaches with a radiotherapy application –

Raldow AC, Chen AB, Russell M et al. (2019) Cost-effectiveness of Short-Course Radiation Therapy vs Long-Course Chemoradiation for Locally Advanced Rectal Cancer. JAMA

Sher DJ, Tishler RB, Pham NL et al. (2018) Cost-Effectiveness Analysis of Intensity Modulated Radiation Therapy Versus Proton Therapy for Oropharyngeal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys.

Sher DJ, Parikh RB, Mays-Jackson S et al (2014) Cost-effectiveness analysis of SBRT versus IMRT for low-risk prostate cancer. Am J Clin Oncol

Examples of health economic modelling approaches with a diagnosis or screening application – please note that the following are illustrative examples based on a brief scan on informative and relevant studies:

Goffin JR, Flanagan WM, Miller AB et al (2015) Cost-effectiveness of Lung Cancer Screening in Canada. JAMA Oncol. 2015 Sep;1(6):807-13. doi: 10.1001/jamaoncol.2015.2472. PMID: 26226181.

Goldie SJ, Kim JJ and Wright TC (2004) Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol.

Mogul D, Zhou M, Intihar P et al. (2015) Cost-effective analysis of screening for biliary atresia with the stool color card. J Pediatr Gastroenterol Nutr.

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By being an MRS Company Partner, Ipsos UK endorse and support the core MRS brand values of professionalism, research excellence and business effectiveness, and commit to comply with the MRS Code of Conduct throughout the organisation & we were the first company to sign our organisation up to the requirements & self-regulation of the MRS Code; more than 350 companies have followed our lead.

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