Delivering a Globally Competitive Precision Medicine Ecosystem for Scotland

[REDACTED]
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On behalf of Health Science Scotland

30th November 2015

Purpose of Paper:

This paper provides additional detail of the content, timescales and funding for the informatics and clinical Exemplars outlined in the original Precision Medicine Ecosystem for Scotland document dated 15th October 2015.

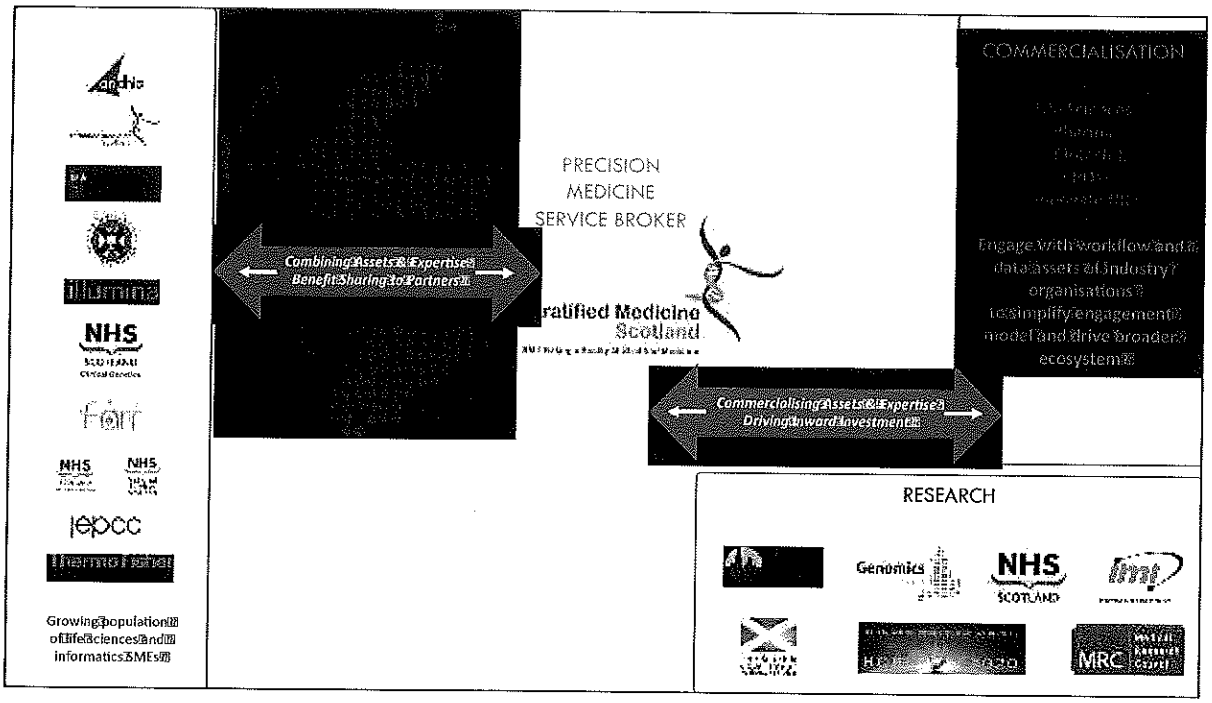
Outline Proposal:

We request strategic investment for the Stratified Medicine Scotland Innovation Centre (SMS-IC). Specifically the investment will secure:

- An outstanding precision medicine platform that will "join up" the broad field of informatics to link detailed biology with human health and disease across Scotland
- Further investment in two flagship nationwide programmes on precision medicine of pancreatic cancer and multiple sclerosis
- A more powerful SMS-IC that aligns outstanding NHS, academic and business assets to drive beneficial change and efficiency.

This proposal is timely as it resonates with Scottish Government Economic Strategy and the new CSO Strategy for Health Research in Scotland. Specifically it:

- Fosters a culture of innovation and research and development within NHS Scotland
- Makes best use of public sector levers and funding to drive change
- Will develop a truly collaborative approach to precision medicine across the whole of Scotland
- Promotes Scotland on the international stage to boost our trade and investment, influence and networks
- Is consistent with Programme for Government 2015/16 that committed to support Innovation Centres to use academic expertise to address real world business issues, helping them to raise their profile with businesses in Scotland and beyond.


PRECISION
MEDICINE
SERVICE BROKER
Combining Assets & Expertise
Benefit Sharing to Partners
ratified Medicine
Scotland
COMMERCIALISATION
Engage with workflow and
data assets of industry
organisations
to simplify engagement
model and drive broader
ecosystem
Commercialising Assets & Expertise
Driving toward Investment
RESEARCH
Genomics
NHS
SCOTLAND
MRC
Growing population
of life sciences and
informatics SMEs

Investment description

Summary of £4M Investment

The summary timeline and breakdown on the required investment is summarised in the table below and further described later in the document.

	1Q 2016	2Q 2016	3Q 2016	4Q 2016	1Q 2017	Total to end Q1 2017
Service Broker Model						
Staff: Network Co-ordinator	34	30.3	30	30	30	179
Staff PM/Contracts Mgr	34	30.3	30	30	30	179
Staff: BD/Sales			41	41	41	123
Staff: QA Mgr			30	30	30	89
Consulting: Design & scope of SBM opportunities	67	69	62	69	69	337
Systems: Implement Service Provider Mgmt System	67	33				100
Systems: Operate Service Provider Mgmt System			7	7	6	20
Legals: Secure agreements in use	5	0	0	0	0	10
Services: Develop engagement model with Service Providers	15	10	10	10	10	80
Systems: Implement Data Asset Catalogue	15	15				50
Systems: Operate Data Asset Catalogue		3	3	3	3	10
Commercial: Develop GxP compliance pack		15			23	38
Website enhancements/online marketing	30	8				38
TOTAL	287	241	217	217	261	1264
Platform Services						
Systems: Implement Clinical Trial Management System	75	75				150.0
Systems: Implement Multiuser LIMS System	38	38	38	38		150.0
Systems: Implement PaaS for Annotation	40	35	40	25		160.0
Systems: Implement Genomic Repository	27	20	20	13		80.0
Systems: Implement Metadata Services	40	40				80.0
Systems: Operate Clinical Trial Management System	1	5	5	5	5	20.00
Systems: Operate Multiuser LIMS System	1	5	5	5	5	20.00
Systems: Operate PaaS for Annotation	5	35	35	35	35	150.0
Systems: Operate Genomic Repository	1	5	5	5	5	20.00
Systems: Operate Metadata Services	1	5	5	5	5	20.0
TOTAL	234	281	151	129	54	850
Federated Analysis						
Systems: Implement federated analysis capability		100	100	100	100	400
Systems: Operate federated analysis capability			50	50	50	150
Systems: Define engagement model for federation		50	50			100
TOTAL	0	150	200	150	150	650
SUMMARY CORE INFORMATICS PROGRAMME	521	672	568	517	465	2764
PRECISION-Panc						
Kick Start Project	50	50				100
Build and Maintain Clinical Data Repository			30.3	30.3	28	81
Genetic Sequencing			174			174
Develop and Implement Patient Registration and Matching tools	40	37	20			97
Critical Systems Support	17.5	21.88	21.88	21.88	21.88	105
Business Development Engagement with Industry (jointly with FMS)			28	28	28.0	84
Set up/obtain/maintain ISO certification of sequencing lab - Jointly with FMS	15	30	15		15	75
TOTAL	123	139	285	78	93	718
Future MS						
Ethics and Regulatory Approvals	4.5					5
Part-funded Clinical Fellow at Glasgow MS Clinic	55.2					55
Collate and store DNA	1.7	1.7	1.7	1.7	1.7	6
Extraction and Sequencing	295.8					295
Additional Data Capacity					16	16
Bioinformatics Analysis					60	60
Business Development Engagement with Industry (jointly with PP)				21.5	21.5	43
Set up/obtain/maintain ISO certification of sequencing lab - Jointly with PP			5		15	20
TOTAL	356	1	6	23	114	520
SUMMARY EXEMPLAR PROGRAMME	479	140	292	99	227	1236
SUMMARY TOTAL BUDGET	1000	812	860	616	692	4000

Informatics Budget request (£2.9M)

The core informatics budget request (£2.8M) would enable the delivery of the workstreams highlighted below and the operation of those services through to March 2017, with the expectation that the Precision Medicine Ecosystem would be established by that date and would be attracting significant levels of commercial income. SMS, through its role as the service delivery vehicle for the ecosystem, would receive a share of revenues allowing it to continue to support the on-going development and delivery of those services beyond March 2017.

Each of the workstreams provides a shared set of informatics services to enable the delivery of multiple precision medicine programs using assets and capabilities from multiple participants in the ecosystem. In essence the cost and benefits are shared across multiple programs. The program examples highlighted below are for Precision Panc and Future MS. Both exemplars demonstrate the use of the ecosystem through the Service Broker Model, the Clinical Platform and the anticipated use of the Federated Analysis to extend cohorts internationally and attract additional funding to Scotland. Assuming we can demonstrate early success, commitment and momentum behind the informatics infrastructure and clinical Exemplars we expect that the Precision Medicine Catapult will provide a level of matched funding to further accelerate commercial adoption throughout the NHS in England and Internationally.

We have highlighted budget and timescale requirements for the three informatics workstreams below. For clarity, functionality delivered through the informatics workstreams are highlighted within the descriptions of the Precision Panc and Future MS exemplars.

For the avoidance of doubt, SMS will prepare full specification, procurement and budget allocation details for each of the informatics workstreams to the SMS Board for approval before work commences.

- *Service Broker Model – enabling the Precision Medicine Ecosystem in Scotland, through the initial establishment and maintenance of a participant programme and service catalogue across all participants. This would be followed by the setup of a business development/sales and solution definition function, to define the combined service offerings for particular projects, and to generate a pipeline of customers/programmes. Finally, a service delivery and project governance framework will be established to deliver the integrated solutions to the customer, having back-to-back service level agreements with the participating service providers, and agreed data access and interchange mechanisms.*

The Service Broker Model is essentially about enabling the commercialisation of precision medicine services that Scotland can offer nationally/internationally and doing so with a model that accelerates our time to market within a competitive global environment and ensures benefit sharing across all the ecosystem participants. Three key sub-components exist -

Service Catalogue – configuration of an online resource of data assets for the Scottish ecosystem partners that are relevant for commercial project delivery. Intention is to make the metadata (description of the data) for these assets available in an open and standards-based manner. This will allow commercial partners to view what Scotland has to offer and enable future ecosystem participants (academic groups and SME's) to highlight their service offerings.

SMS will make this capability as self-service as possible both for commercial partners (customers) and for ecosystem participants (suppliers). Inclusivity for participants within Scotland and visibility for commercial partners are the key drivers.

Service Delivery and Governance – critical to the successful operation of the precision medicine ecosystem is that delivery of a project or set of services is as seamless as possible and that we present ourselves as easy to do business with.

SMS will provide a delivery and programme management function on behalf of the Scottish ecosystem. We will define revenue sharing arrangements between ecosystem participants and configure instrumentation within the workflow of projects to provide governance and audit reporting for the revenue sharing arrangements between ecosystem participants.

Solution Definition – from the service broker and service delivery components SMS will configure specific customer solutions detailing deliverables, timescales, service level agreements, risks and costs. We will provide an account management interface to the customer and a project management interface to the ecosystem participants.

Summary budget and timeline for the Service Broker Model

Service Broker Model – Dec 15 – March 17 (15 months) £1264K

For SMS, the maintenance and curation of the Service Broker Model will be an on-going cost which beyond 15 months from December 15 – March 17 will be met through future revenue sharing arrangements. In essence the funding for the Service Broker Model allows us to configure and resource this capability to the point that it is operationally proven.

- *Platform Services – the validation of new diagnostic tests based on complex bioinformatics processing pipelines is currently problematic, and may rely on 'big data' infrastructures which are not easily available to, for example, NHS customers; existing capability at SMS will be extended to support a development, test, validation and production deployment workflow, supporting instrumentation and comparison of multiple genomic pipelines to inform procurement decisions, and to support clinical/regulatory validation and subsequent use of novel tests during patient care.*

SMS will implement and configure a number of data and informatics services to enable customers and ecosystem partners to bring their diverse bioinformatics pipelines for test, validation and deployment.

SMS will configure data management services to enable the linkage of data workflow across the ecosystem (including customer data workflows) for a particular customer programme in an automated, repeatable and auditable manner.

SMS will provide metadata services to allow project specific datasets to be constructed from customer data and ecosystem participant data alongside ontology matching services to enable direct integration with diverse data sources and de-identification services to ensure confidentiality of data used within a particular project.

SMS will provide a number of end user application services to facilitate translation from research into practice such as molecular reporting and molecular MDT services.

Summary budget and timeline for Platform Services

Platform Services – Dec 15 – March 17 (15 months) £850K

SMS will prepare full specification, procurement and budget allocation details to the SMS Board for approval before work commences.

For SMS, the maintenance and enhancement of the Platform Services will be an on-going cost which beyond 15 months from December 15 – March 17 will be met through future revenue sharing arrangements.

- *Federated Analysis – having a single entity act as the governance vehicle for interoperability and service level definition will enable and simplify local and international collaborations. Work will be undertaken to develop protocols and supporting systems for such analyses, based on emerging standards from the Global Alliance for Genomics and Health.*

SMS will implement a capability for federated analysis. Federated analysis describes the ability to share data for distributed analysis without physically sharing it. At its core, it is about making connections between distributed groups and enabling them to study important sample data in a collaborative fashion. We are currently running a PoC on this capability with collaboration between SMS and genomic centres in Australia, England, Russia, China and the United States. This PoC is also endorsed by the Global Alliance for Genomics and Health.

Our intention is to 'productise' the results from the PoC and implement as an available service for the ecosystem. We know that commercial partners want to bring their data assets into particular projects but in many cases are unable to 'move them' due to size, governance or costs reasons. The federated analysis services will enable this barrier to be overcome.

Summary budget and timeline for Federated Analysis

Federated Analysis – Apr 16 – March 17 (12 months) £650K

SMS will prepare full specification, procurement and budget allocation details to the SMS Board for approval before work commences.

For SMS, the maintenance and enhancement of the Federated Analysis will be an on-going cost which beyond 12 months from April 16 – March 17 will be met through future revenue sharing arrangements.

In all three informatics workstreams, the budget requested will be governed by the SMS Board. As well as the implementation of core functionality we envisage that participants within the ecosystem will be provided with funding to enable their services and data assets to be made available in a modern and consumable fashion.

Exemplar Projects (£1.2M)

To lead the international market Scotland critically needs to exemplify delivery of some high profile projects, thus bringing *Precision Medicine into Practice.* We propose two pivotally poised projects to be accelerated for this purpose Precision Panc and Future MS. The budget requirements highlighted include elements for sequencing costs, employing both the Illumina platforms, owned and managed by Edinburgh and Glasgow Universities, and the Ion torrent Platforms within SMS-IC. Additional elements include the establishment of clinical data repositories and molecular diagnostic tests.

1). 'Precision Panc' *is a national initiative (led by [REDACTED], University of Glasgow) which is developing mould-breaking molecular diagnosis and the consequent multi-disciplinary treatment of pancreatic cancer. This needs to become part of routine clinical services for NHS Scotland patients.* ***(£716k requested).***

Pancreatic cancer is currently the 4th leading cause of cancer death in Western societies, and is predicted to become the 2nd leading cause within a decade. Prognosis is poor with median survival 6 months and 90% of patients succumb within one year of diagnosis. There has been little improvement in patient outcomes over the last half century, largely due to considerable interpatient variation in disease. The combination of poor survival rate and significant variation between patients in the same cancer also prevents efficient allocation of patients to clinical trials which would ultimately improve outcomes. The reason for that is that a specific drug may have potential benefit in one cancer sub-type but it may be necessary to screen 100 patients or more to find that one patient. This is prohibitively expensive and time consuming. The conventional clinical development programme design therefore fails these patients.

PRECISION-Panc is a new initiative which aims to accelerate scientific discovery in this critically important area as a development platform designed to coordinate world-leading pancreatic cancer research whose mission is to identify, test and then implement stratified therapeutic approaches which will improve overall outcomes for patients.

The initiative is being led by [REDACTED], Glasgow. The initiative is structured as a consortium of approximately 100 clinical and research members from across five CRUK centres (Glasgow, Manchester, Cambridge, Oxford and London).

The project is intended primarily to characterise rapidly an individual patient's pancreatic cancer and introduce each to the appropriate one of a number of available clinical trials designed to treat that specific tumour type. In this way recruitment to clinical trials is rendered much more efficient with consequent reduction is costly up front expenditure on screening. This can be viewed as a valuable service to patients who have an enhanced option to be treated early with novel therapeutic agents and also as a valuable service to the research community and to commercial drug developers who are willing to pay enhanced Clinical Trials fees in return for assured patient recruitment in this challenging area.

Stratified Medicine Scotland- Innovation Centre will provide the necessary screening and informatics support to enable the project to be successful

This initiative will therefore provide the following benefits:

- Improved patient outcomes in Scotland and elsewhere
- Enhanced inward flow to Scotland of Clinical Research with associated funding
- Places Scotland at the centre of a network of world class research in pancreatic cancer
- Supports the building of the Scottish Precision Medicine Ecosystem

Proposed Workflows

1. Previously diagnosed Pancreatic Cancer patients will be referred to PP and entered into an umbrella clinical trial protocol (PRIMUS)
2. A tumour biopsy is shipped to PRECISION-Panc
3. Tissue sample is logged, labelled and tracked through the process
4. DNA is extracted and genomic screening is conducted in parallel with other laboratory assessments to fully characterise the tumour
5. PP Multi-Disciplinary Molecular Diagnostic Team assesses the patient and recommends action to be taken:
    a. Entry into appropriate clinical trial in Scotland
    b. Entry into appropriate clinical trial ex-Scotland
    c. Continue with existing Standard of Care

Prerequisites and assumptions

1. Identification and implementation of extensive portfolio of clinical trials (requires both strong reputation and formal marketing of facility). Two major international pharmaceutical companies have already indicated readiness to place trials within the framework. It is anticipated that other companies will follow suit once proof of concept can be demonstrated. Precision Panc will also be run with a US centred component. It is important that the Scottish/UK program accelerates relative to the US, as competition for commercial funding will apply.
2. Genetic analysis and other screening procedures with turnaround time <2 weeks
3. Development of self-sustaining commercial business model (development of appropriate fee structure for all services including screening, diagnosis and study referral)
4. Underpinning by fully developed systems and process to ensure effective operation

5. It is assumed that seeding funding is required to initiate the project, which will ultimately require to be self-funded through fee generation. Income will be generated from clinical trials fees which will be pitched at premium rate for high quality fully characterised patients (thus removing the substantial risk of inadequate patient recruitment)
6. Once processes and systems are established and validated, other suitable cancers or even other therapeutic areas will be identified which will fit this model and the clinical trials patient recruitment services described herein will be actively marketed to interested pharmaceutical companies.
7. Discussions have already been initiated with SMS-IC around a potential genetic sequencing opportunity for patient recruitment to trials in oesophageal cancer and ovarian cancer. The systems and processes built for PRECISION-Panc would be re-purposed for this new indication and would generate additional clinical trials income for Scotland
8. NRS industry liaison and feasibility assessment processes will not be directly affected in any adverse way and it is anticipated that the strength of their clinical trials offer to industry will be enhanced by the availability of these premium priced expert services from Scotland
9. PRECISION-Panc will provide opportunities to enhance basic research activities in addition to the clinical drug development support activities noted here. These additional avenues of research activity have not been considered in this description of clinical research support.

Implementation Plan and Associated Investments

Component Project	**Timeline**
Kick Start project designed to compile existing data. Summary outcomes: • The core Precision-Panc database will be established and seeded with existing data on pancreatic cancer cases from previous research • Case data will be linked and cross-referenced with reference data from ClinVar or other relevant sources • Prototype decision support tools for Molecular Multi-Disciplinary Team (MDT) clinical meetings will be demonstrated • Validation and iterative testing of proposed decision support tools will be conducted with real end users • Prototype administration and tracking of research participants and diagnostic service customers will be developed • We will demonstrate how the analytical platform can be used to provide research environment and secure data sharing for industrial customers	6 months
Clinical Data Repository • Match patients with known biomarkers of pancreatic cancer • Updating of library as new biomarkers are validated • On-going maintenance and licensing of database constructed during kick start project	15 months with on-going support funded through commercial revenues

Critical process: Genetic Sequencing • Designated NGS process for genetic screening is Illumina technology (SGP Edinburgh and Glasgow) employing SMS-IC staff as needed • Estimated that at full capacity 300 samples will be screened per annum • Laboratory Management • Variable but increasing recovery of costs via clinical trials fees after year 1 • DNA extraction • Method validation to clinical DX specification (UKAS to ISO15189 standard) • Integration of HiX units within SMS compute cluster	15 months with on-going support funded through commercial revenues
Patient Entry process • Development eCRF • Patient registration process • Consent Management and trial matching tools (or return to standard of care)	12 months
Decision tools and processes for MDT • Prototype tools developed to final specification with feedback from actual users in Kick Start phase	15 months with on-going support funded through commercial revenues
Underpinning LIMS/CTMS • Critical systems and process development within platform infrastructure • Required to match patient registration with samples and subsequent • Generation of extracted DNA and other derived biological substances • Ensures project management, quality control, and all compliance and regulatory standards • Triggers invoicing and payment of fees	15 months with on-going support funded through commercial revenues
Supporting Functions • PM: overall management of processes, to budget, quality and time, engagement with stakeholders. Interface with finance function to ensure appropriate inflow of funds and dispersal according to agreed contractual milestones • QA: Quality Management System, Regular Process Review and Monitoring of standard of output • Finance: Control of project finance, Invoicing for services rendered, payment of invoices received • External programme management and support for informatics systems	15 months with on-going support funded through commercial revenues
Marketing/Business Development • Enables project to become self -funding by attracting	15 months

commercial sponsors and additional referral sites • Continual replenishment of Clinical trials portfolio is required to maintain the recruitment model at high level of effectiveness	with on-going support funded through commercial revenues

(2) The Future MS project. The project has 'many elements of the eco-system in place (academic leadership, [REDACTED], University of Edinburgh, sequencing from SMS-IC and Edinburgh, clinical engagement through NHS Lothian, NHS Grampian, NHS Tayside and NHS Greater Glasgow and Clyde, buy-in from the charitable sector and clinical community, industry partnership with Biogen, and a growing interest from other healthcare providers). The opportunity exists to accelerate both the commercial scope and the number of sequenced patients and market this exemplar globally during 2016 ***(£520k requested).***

Multiple Sclerosis (MS) is a chronic and incurable disorder that reduces life expectancy by 5-15 years. 85-90% of incident UK cases have a relapsing-remitting disease course at onset characterised by periods when clinical symptoms emerge and then resolve after a median of 19 years, a phase of progressively accumulating irreversible disability emerges called secondary progressive MS. The remaining 10-15% of incident cases have a progressive disease course from onset (primary progressive MS). In addition to between-subject heterogeneity in the timing of emergent progression, there is also significant between-subject heterogeneity in the rate of disease activity whether measured by relapse-frequency, or the rate of disease progression. This negatively impacts our ability to make prospective decisions about best management.

MS has a particular relevance for Scotland. Prevalence rates vary around the UK. It is estimated that the number of people with MS in Scotland is 212 per 100,000. This compares with an estimate of 165 per 100,000 in England. Prevalence in the north of Scotland is particularly high with a 2009 study of north east Scotland founding the level per 100,000 people to be 229 in Aberdeen, 295 in Shetland and 402 in Orkney. The Global prevalence of MS is approximately 2.5 million people [USA; ~400,000, UK ~107,000; Scotland ~10,700]. It is the leading cause of acquired disability in the younger population in the industrialised world; 85% of prevalent cases are of working age. The precise aetiology of MS is unknown.

Currently there is no objective evidence based method for determining which patients with MS (pwMS) should receive disease-modifying treatment (DMT). Decisions about when to start treatment and which DMT to use currently represent a "best guess" risk/benefit judgment based on (i) prior disease activity in a given pwMS (a predictor of future personalised disease activity), and (ii) clinical trial data describing aggregate treatment-response in the "typical" patient. Although "personalised", this strategy is *reactive* and therefore results in potentially preventable relapses, lost "brain-protection time", and exposure to unnecessary risk. There is therefore a need for predictive tools – derived from real-world, not trial datasets - that can provide at diagnosis a personalised estimate of future disease activity. Overall DMT prescribing rates in the UK are low (*c.*12% pwMS) as compared to European (*c.*50-60% pwMS), Australian, and North American practice. Moreover, a substantial proportion (*c.*50-75% in recent audit) of newly diagnosed pwMS

in Scotland do not receive early-treatment with DMT and are managed expectantly. This creates a unique opportunity to develop natural history predictive tools in the Scottish MS population.

In summary, today we are unable to predict, at diagnosis, which Scottish patients will have benign, aggressive or intermediate disease course. The need is for integrated clinical, imaging and genetic predictive tools to inform individualised better clinical management and decision-making.

FutureMS is a recently launched project under the aegis of SMS-IC aimed at developing an evidence-based predictor for disease progression in pwMS. This will deliver to the clinic a tool set to allow personalised and *proactive* DMT use in MS that will improve the quality of clinical decisions around risk/benefit relationships with existing treatment options. A major additional outcome of this project is to deliver NHS data integration that in turn will allow the creation of "point of care" clinical tools to both streamline and guide decision-making; this will support a standardised approach across diverse healthcare environments, enabling national audit and driving up standards of care delivery.

The project is being led by [REDACTED] at Edinburgh University. The project is a pan-Scotland enterprise engaging Consultant Neurologists in NHS Grampian, Lothian, Greater Glasgow and Clyde and Tayside in the recruitment of the planned 515 patient cohort over a 2-year period (representing approximately 50% of the new MS diagnoses across Scotland). The scope of work at these centres includes patient recruitment, baseline clinical sample collection, processing and local storage and MRI imaging. Industry engagement has been part of this project from its outset with *c.*40% funding being provided funding being provided from one industrial partner. The project offers benefits to healthcare providers, to the patients and to industry.

The project's current scope is to develop a set of predictive tools based on a combination of clinical measures and genetic sequencing of SNP, CNV and RNA modalities aligned with evidence of disease progression based on comparisons of baseline and 12 month MRI scans from pwMS. Limitations to existing funding have precluded any deeper analysis of the genetic signatures of the patients in this cohort. Additional clinical samples will be collected and maintained in the Edinburgh Wellcome Trust CRF Biorepository.

The requested funding would be used to develop a significant extension to the FutureMS Project with the following enhancements to the Project's scope:

- Undertake whole genome sequencing (WGS)on a significant element of the FutureMS cohort. This represents a major enhancement of the "genomics dataset" of this cohort and provides a complete 360-degree perspective of all genetic sequence differences contributing to disease progression in the MS cohort. This is greatly additive to the SNP, CNV and RNA expression data that are already being collected from this patient cohort.
- Understanding the genetic component of differences between "polar extremes" of patients in the FutureMS cohort. Specifically, addressing differences between relapsing and progressive subgroups of the cohort.
- Providing the ability to contribute these data into wider genetic analyses on a wider international front through the use of federated databases analyses under appropriate secure governance.
- Developing and marketing a contractual engagement with multiple industry partners to engage industry on a wider base than currently the case. This envisions making elements of the phenotype and genotype datasets available to industry partners and supporting industry engagement of cohort members in future clinical trials (patients will be optionally consented for recontact).

Proposed Workflows:

1. Patients consented into the FutureMS study will have sufficient blood samples withdrawn at their base visit to support WGS sequencing in addition to the currently planned bioassays and sequencing studies.
2. Samples for WGS will be maintained in the WTCRF Biorepository until the conclusion of the patient's second visit and determination of the extent of disease progression. At this point it will be possible to characterise the patients into progressive or relapsing subgroups.
3. Sub-cohorts of approximately 75 patients from each of the subgroups will be selected and their DNA samples retrieved from the Biorepository.
4. WGS will be undertaken on a total of 150 patients. This would cover *c.* 30% of the FutureMS cohort.
5. A bioinformatic analysis of the WGS dataset to identify additional genetic associations with disease progression.
6. Development of Ecosystem model to support engagement of UoE WTCRF, Fios Genomics, NRS Scotland and EPCC as ecosystem partners with master service agreements in place and service catalogues/service level agreements developed.
7. Development and testing of federated database analysis capabilities in conjunction with industry partners
8. Active prospecting of the FutureMS cohort and its datasets to engage additional pharma partners. Subsequent engagements will result in either extension of the FutureMS cohort's scope and duration (patient numbers and extent of clinical follow through) and/or recruitment of pwMS into pharma funded clinical trials in conjunction with the NRS Clinical Trial Network.

Prerequisites:

1. Engagement with Pharma and Biotech organisations with an interest in the MS field to gauge perceived value of this cohort. To date we are aware of three pharma organisations (identities not disclosed as commercially sensitive who have expressed interest in the FutureMS cohort.
2. Securement of agreement from Biogen that additional third parties could be engaged with around this cohort. Initial dialogues with Biogen have indicated that this may be an acceptable route forward.
3. Funding will be required to undertake the above listed activity streams as these are currently outwith the scope of the current FutureMS project.

Implementation Plan and Associated Investments

Component Project	Timeline
Ethics and tissue bank approval: • Draft and submit extension to FutureMS' ethics approval to support WGS related research. • Secure approval from WTCRF tissue bank for release of DNA samples for WGS activity	3 months elapsed
Sample collection: • Collate DNA samples over course of clinical recruitment • Process and store in WTCRF	15 months with on-going support funded through commercial revenues
Sample Extraction and sequencing: • Review cohort progression data • Identify polar opposite sub-cohorts for WGS • Retrieve samples from WTCRF tissue bank • Extract DNA • Undertake WGS at 30X coverage on Ion Torrent platform • Additional data storage/processing provision • Method validation to clinical DX specification (UKAS to ISO15189 standard)	15 months with on-going support funded through commercial revenues
Bioinformatic Analysis: • Undertake pre-processing, alignment and SNP calling • Undertake SNP integration and merging • Identify non coding/coding variants not found in existing databases. Test for segregation of identified variants with disease phenotype	15 months with on-going support funded through commercial revenues
Establish PM Ecosystem model:	Year 1
Establish federated database analytics capability:	15 months with on-going support funded through commercial revenues
Secure Pharma engagement with FutureMS cohort:	On-going
Engagement of Cohort through NRS	15 months with on-going support funded

	through commercial revenues

In summary, total funding of £4 million is requested (comprised of £2.8M for the Scottish Precision Medicine core informatics and £1.2M to accelerate two exemplar programmes). The £4M funding will be pivotal to accelerate Scotland's progress to lead in precision medicine globally. The investment will enable us optimally to drive and exploit the opportunity afforded by stronger collaboration between existing partners, including NHS Scotland. It will enable alignment with the goals and aims of industry partners, including large diagnostic and pharma companies as well as Scottish SMEs.