Study Title: A prospective long-term observational study in patients with monoclonal gammopathy of undetermined significance

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Chief Investigator: **Dr Karthik Ramasamy**, Consultant Haematologist & Associate Professor, Oxford University Hospitals NHS Foundation Trust & RDM, University of Oxford, Cancer Centre, Churchill Hospital, Old Road, Headington, OX3 7LE

Email: karthik.ramasamy@ndcls.ox.ac.uk

Investigators: **Prof Guy Pratt**, Professor of Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham

Email: g.e.pratt@bham.ac.uk

Dr Ross Sadler, Clinical Lead, Oxford University Hospitals NHS Foundation Trust, Immunology Laboratory, Churchill Hospital, Old Road, Headington, OX3 7LE

Email: rosssadler@nhs.net

Dr Kassim Javaid, Norman Collisson Senior Research Fellow, Associate Professor in Metabolic Bone Disease, Nuffield Centre of Orthopaedics, University of Oxford

Email: kassim.javaid@ndorms.ox.ac.uk

Dr Constantinos Koshiaris, Nuffield Department of Primary Care Health Sciences, University of Oxford

Email: constantinos.koshiaris@phc.ox.ac.uk

Prof Christopher Bunce, School of Biosciences, University of Birmingham, Birmingham, UK

Email: C.M.BUNCE@bham.ac.uk

Prof Warwick Dunn, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

Email: warwick.dunn@liverpool.ac.uk

Dr Martin Kaiser, Research Team Leader, Genetics and Epidemiology, The Institute of Cancer Research & Consultant Haematologist, The Royal Marsden NHS Foundation Trust, Sutton, Surrey, SM2 5NG

Email: Martin.Kaiser@icr.ac.uk

Dr Stella Bowcock, Consultant Haematologist, King's College Hospital, Denmark Hill, London, SE5 9RS

Email: stella.bowcock@nhs.net

Dr Fenella Willis, Consultant Haematologist, St George's University Hospitals NHS Foundation Trust, Tooting, London

Email: fenella.willis@stgeorges.nhs.uk

Dr Jenny Bird, Consultant Haematologist, University Hospitals Bristol and Weston NHS Foundation Trust

Email : jenny.bird@uhbristol.nhs.uk

Dr Simon Stern, Consultant Haematologist, Epsom and St Helier University Hospitals NHS Trust

Email: simon.stern@nhs.net

Prof Supratik Basu, Royal Wolverhampton Hospitals NHS Trust, Haematology and Oncology, Wolverhampton, UK

Email: supratik.basu@nhs.net

Dr Grant Vallance, Oxford University Hospitals NHS Foundation Trust, University of Oxford, Cancer Centre, Churchill Hospital, Old Road, Headington, OX3 7LE

Email: grant.vallance@ouh.nhs.uk

Dr Gaurav Agarwal, Oxford University Hospitals NHS Foundation Trust, University of Oxford, Cancer Centre, Churchill Hospital, Old Road, Headington, OX3 7LE

Email: gaurav.agarwal2@nhs.net

Sponsor: Oxford University Hospitals NHS Foundation Trust

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Chief Investigator Signature:  **Date:** 19/8/2022

No potential conflicts of interest.

Confidentiality Statement

This document contains information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

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1. KEY CONTACTS:

Chief Investigator	Dr Karthik Ramasamy, Consultant Haematologist & Associate Professor, Oxford University Hospitals NHS Foundation Trust & RDM, University of Oxford, Cancer Centre, Churchill Hospital, Old Road, Headington, OX3 7LE Email: karthik.ramasamy@ndcls.ox.ac.uk
Sponsor	Oxford University Hospitals NHS Foundation Trust, Research and Development Department, Joint Research Office, Second Floor, OUH Cowley, Unipart House Business Centre, Garsington Road, Oxford, OX4 2PG
Funder(s)	Cancer Research UK Cancer Centre Oxford and the Medical Research Council
Trial Coordinator	Late Phase Haematology Research Team, Churchill Hospital, Headington, Oxford, OX3 7LE Email: secure@ouh.nhs.uk
Statistician	Constantinos Koshiaris
Data Manager	Grant Vallance
Committees	Trial Management Committee Chair: Karthik Ramasamy Data Management Committee Chair: Grant Vallance Trial Steering Committee Chair: Richard Kaplan

2. LAY SUMMARY

Multiple Myeloma (MM) is a rare blood cancer affecting over 5000 people a year in the UK. All cases of myeloma start with a condition called monoclonal gammopathy of undetermined significance (MGUS). MGUS occurs in approximately 3.2% of people aged 50 and over. Only a small proportion of these people – around 1% each year - will develop myeloma. Most people with MGUS have no symptoms, but a small number of people will suffer complications. This group are referred to as having monoclonal gammopathy of clinical significance (MGCS).

People with myeloma frequently experience long delays in diagnosis; the delays are longer than for any other cancer. Although we know that MGUS leads to myeloma, most cases of MGUS are only found 'incidentally' when the person is having blood tests for something else. And the people who have MGUS do not have consistent testing or follow up. This situation means that 80 – 90% of people who are diagnosed with myeloma did not have an earlier MGUS diagnosis.

Earlier diagnosis of myeloma might be possible with better understanding of MGUS and how it should be monitored. The SECURE study will help with this. We will observe the rate at which people with MGUS progress to a diagnosis of myeloma. It will further our understanding of screening, diagnosis, and monitoring patterns of people with MGUS and MGCS in the UK.

The study aims to find out more about the role of family history and demographic factors in the development of MGUS. It will also find out more about the psychological impact of an MGUS diagnosis and individual quality of life.

Patients with MGUS will be identified by their clinical care team and invited to participate in the SECURE study. Participants will be required to answer surveys and questionnaires annually for a period of 5 years or until their disease changes. It will recruit people from 20 NHS sites in the UK. Patients will be asked to provide blood samples. SECURE is funded by Cancer Research UK (CRUK) and the Medical Research Council (MRC).

3. SYNOPSIS

Study Title	A prospective long-term observational study in patients with monoclonal gammopathy of undetermined significance
Internal ref. no./short title	**SECURE Study: Long-term observation in Monoclonal Gammopathy**
Study Registration	
Study Design	Prospective Cohort Study
Number of Sites	20 for patient recruitment and sample collection
Study Participants	MGUS patients
Planned Sample Size	2000
Planned Study Period	September 2022 – September 2029

	Objectives	Outcome Measures
Primary	Progression rate to MM	Incidence rate of MM during observation
Secondary	To determine the monitoring patterns of patients with MGUS and the rationale behind them	Qualitative analysis: Remote or face to face monitoring by Secondary Care Primary Care based monitoring Direct lab based monitoring
Secondary	Screening for MGCS	Quantitative analysis: Tests/ clinical evaluation for MGCS
Secondary	Understanding routes to MGUS diagnosis	Qualitative analysis: Screening vs Incidental
Secondary	To understand family linkage in relation to MGUS	First and second-degree family history of plasma cell dyscrasia No family History
Secondary	To use questionnaires to better understand the impact of MGUS diagnosis on QoL post diagnosis (annual)	EORTC QLQ-C30
Secondary	To understand the underlying psychological impact and needs after diagnosis and post-diagnosis.	PHQ-9, GAD-7, HAI, IUS, , PCL-5
Exploratory	Health resource utilisation	EQ5D annually HE analysis with primary care and HES data
Exploratory	Determine if S1P and acetyl carnitine have value as a predictive biomarker for progression to MM	Correlate their rate of change with progression
Exploratory	Identify new biomarkers to detect early disease progression	Mass spectrometry Genomic profiling
Exploratory	Identify germline genetic variants associated with risk of developing MGUS and/or MM	Germline genetic profiling

4. ABBREVIATIONS

Commented [BR(O1]: To be updated

2-HG	2-hydroxyglutarate
BM	Bone marrow
BRC	Biomedical Research Centre
CI	Chief Investigator
CPRD	Clinical Practice Research Datalink
CRAB	Hypercalcaemia, renal insufficiency, anaemia, and bone
CRF	Case Report Form
CRP	C-reactive protein
CRUK	Cancer Research UK
CT	Computerised tomography
DMG	Data Management Group
DOB	Date of Birth
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
FDG	Fluorodeoxyglucose
FLC	Free light-chain
GCP	Good Clinical Practice
GP	General Practitioner
GWAS	Genome-wide association studies
HES	Hospital Episode Statistics
HRU	Health resource utilisation
HTA	Human Tissue Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	Institute of Cancer Research
ID	Identification
IgM	Immunoglobulin M
IMWG	International Myeloma Working Group
IP	Intellectual Property
LDH	Lactate dehydrogenase
MDT	Multidisciplinary team
MGCS	Monoclonal gammopathy of clinical significance
MGP	Myeloma Genome Project
MGUS	Monoclonal gammopathy of unknown significance
MM	Multiple myeloma
M-protein	Myeloma protein
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MRN	Medical record number

MS	Mass spectrometry
NHS	National Health Service
OUH	Oxford University Hospitals
OUHFT	Oxford University Hospitals Foundation Trust
PC-B	Phenome Centre-Birmingham
PET	Positron emission tomography
PI	Principal investigator
PIS	Participant information sheet
PTM	Post-translational modification
QoL	Quality of life
REC	Research Ethics Committee
S1P	Sphingosine-1-phosphate
SMM	Smoldering multiple myeloma
SOP	Standard operating procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WB DW	Whole-body diffusion-weighted
WIMM	Weatherall Institute of Molecular Medicine

5. BACKGROUND AND RATIONALE

Monoclonal gammopathy of undetermined significance (MGUS) is the expansion of a plasma cell clone and earliest clinically detected precursor to multiple myeloma (MM). As all cases of MM are preceded by MGUS[1], but not all MGUS transforms to MM[2], MGUS is a *bona fide* pre-malignant state and disease model to study cancer initiation and progression.

Since its first description in 1978, MGUS has been labelled a condition of 'undetermined significance'. In the fifty years that have followed, the study of MGUS has largely been limited to retrospective single-time-point analyses. Whilst individually informative, there have been few large-scale investigations with ability for longitudinal monitoring, which is required to build a cohesive understanding of the condition. In SECURE, we aim to establish the largest MGUS prospective cohort study in the UK to explore the clinical, biological, and patient significance of MGUS.

5.1. Understanding the clinical significance of MGUS

Despite high prevalence in the general population[3], there is currently a lack of robust evidence supporting optimal clinical management of MGUS. For example, whilst the International Myeloma Working Group (IMWG) advocate specific monitoring frequencies[4], prospective data showing the value of routine MGUS follow-up is lacking[5]. Accordingly, a recent pattern of care

study found great variability in clinical management of MGUS between clinicians, with around 50% concordance to guidelines[6]. In order to inform evidence-based and consistent best practices of MGUS screening and monitoring, prospective studies are required to understand MGUS epidemiology, clinical correlates, and patterns of progression.

Further study is warranted to better understand risk factors for MGUS development. Currently, our understanding is limited to few population-based cohort studies conducted in the USA[7] and Iceland[8]. Whilst studies have consistently shown males[3], African Americans[9] and the over 50 years old population to be at higher risk of developing MGUS[10], an understanding of additional risk factors is scant and has been inconsistent between studies[11]. A UK-based prospective cohort study would clarify the clinical population at highest risk of MGUS, with two intended outcomes. Firstly, this work could suggest novel scientific hypotheses; for example, the epidemiological link between MGUS and autoimmune disease[12] suggests common mechanisms of immune dysfunction that remain to be explored. Secondly, this understanding may be leveraged to target personalised screening for MGUS to the at-risk population in the future.

Understanding the clinical correlates of MGUS is required to improve patient outcomes. There are a number of non-malignant manifestations associated with, or secondary to, MGUS, including amyloidosis, infections, osteoporosis, renal failure and neurological diseases[5]. This population is referred to as having monoclonal gammopathy of clinical significance (MGCS) and have a significantly higher incidence of death[13]. Whilst MGUS management is largely focused on monitoring for progression, these studies suggest there is an urgent need to better manage health of MGUS patients more holistically. Improved knowledge of comorbidities in MGUS would enable improved detection and management of these clinically associated diseases, but also suggest disease populations that may have higher rates of MGUS[5]. For example, we recently found that 1 in 13 patients with a fragility fracture have underlying MGUS, suggesting a clinical population that could be targeted for routine MGUS screening[14]. Therefore, a prospective study understanding the clinical correlates of MGUS is expected to lead to earlier diagnosis of both MGUS and associated conditions and improve patient outcomes.

Prospective studies are required to understand the value of MGUS monitoring and patterns of progression. Firstly, whilst MM patients with a previous diagnosis of MGUS have better overall survival (hazard ratio 0.9)[15,16], no prospective studies have yet validated this to be due to MGUS monitoring, and in fact most MGUS patients with symptomatic progression are diagnosed incidentally (**Figure 1**; problem 1) and not due to scheduled follow-up[17]. Secondly, improved knowledge of patterns of MGUS progression to MM are needed to inform monitoring practices. Given population-level MGUS screening would be impractical and expensive, research is required to understand clinical symptoms. However, the need to regularly monitor a higher number of patients with MGUS would place a huge burden on GPs (Figure 1; problem 2). Whilst the average rate of progression from MGUS to MM is widely cited as 1% per year,

risk varies within the MGUS population[18] and can even change during the clinical course[2]. A UK-based prospective study would, at a basic level, define the rate of MGUS progression to MM in a local cohort. Furthermore, the proposed study would give opportunity to trial the performance of various MGUS risk stratification models. For example, the Mayo Clinic MM Group's model showed that three clinical parameters (the size of the M-protein, type of M-protein, and presence of an abnormal FLC ratio) could define subpopulations with a 20-year progression risk ranging from 5% (no risk factors) versus 58% (three risk factors). Prospective study could both validate the clinical utility of known models, and additionally suggest further clinical correlates of progression. This understanding will enable evidence-based tailoring of MGUS monitoring frequencies in the UK population.

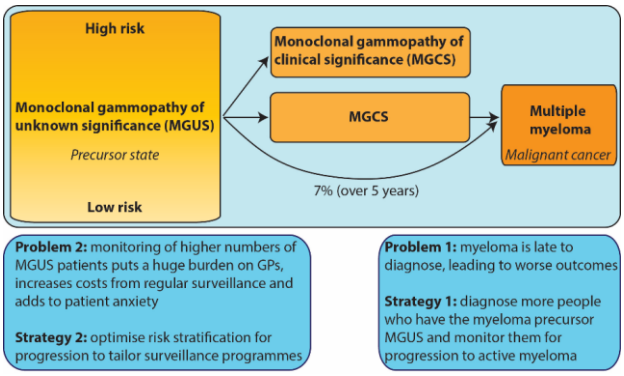

Figure 1. MGUS progression to MGCS and/or myeloma, problems and potential strategies

Overall, better understanding the clinical significance of MGUS through a prospective UK-based trial is intended to answer long-standing basic questions with highly relevant clinical implications. In summary, the proposed project will increase our understanding of who gets MGUS, suggesting populations to target for screening. After diagnosis, study of the clinical manifestations of MGUS will suggest best clinical practices to better manage complications in a minority of MGUS patients. Finally, we seek to understand the rate and clinical correlates of MGUS progression, in order to inform monitoring guidelines in the UK.

5.2. Leveraging MGUS biology to study premalignant cancer evolution

The study of MGUS biology could highlight mechanisms and markers of cancer initiation and progression. As MGUS is the earliest clinically detectable precursor to MM, genomic studies have the potential to understand the roots of MM initiation[19]. In parallel, study could identify biomarkers with clinical value for risk stratification. Currently, serum paraprotein and free light chain quantification are widely used as markers of tumour volume; however, utility is limited in non-paraprotein secreting MGUS and MM, and secretory capacity of a plasma cell clone can change over the course of disease. Novel biomarkers that can better reflect disease activity and aid in clinical monitoring of MGUS may suggest are urgently required. To this end, we propose to study MGUS biology with three tools: genomics, metabolomics and paraprotein mass spectrometry.

The proposed project will investigate germline risk of MGUS. There is a 2-4-fold increased risk of MGUS and MM in individuals with a family history of these conditions[20], suggesting a heritable component. A recent meta-analysis of three MGUS genome-wide association studies (GWASs) analysing 992 patients and 2900 controls[21] highlighted 10 MGUS risk loci (some unique to MGUS and others overlapping with MM risk loci[22]). This preliminary literature suggests that GWAS can highlight genomic loci associated with MGUS initiation and progression. However, statistical power to detect associations has been limited by the relatively smaller scale of MGUS GWASs, compared to larger-scale studies that have highlighted multiple loci predisposing to risk of myeloid malignancies[23,24]. In the proposed project, we have setup an academic collaboration with the Myeloma Group in the Division of Genetics and Epidemiology at The Institute of Cancer Research (ICR), who have a track record in the discovery of germline risk variants for MM. We will characterise germline genetic variants in study participants using state-of-the-art methodology at the end of the planned observation period to identify variants associated with and potentially predictive of MGUS development and progression to MM. The ICR have an ongoing programme focusing on functional validation of germline risk loci[25], which is expected to inform interpretation of findings generated via SECURE and support development of individualised genomic stratification tools.

SECURE will test the clinical utility of a targeted sequencing panel for genomic risk stratification of MGUS. A growing body of literature supports MGUS as a genetically advanced state, although there are currently no genomic tests used to assess MGUS clinically. We and collaborators recently developed the Myeloma Genome Project (MGP) targeted sequencing panel, which captures 228 bespoke genomic regions to identify the main translocations, mutations, and copy number abnormalities in MM (Sudha et. al., in press). Recent work has shown that stable and progressive MGUS exist as two distinct genetic entities, with the latter characterised by the presence of myeloma-defining genomic events[26], suggesting the potential value of MGP Panel as a clinically cost-effective yet comprehensive assay for genomic risk stratification of MGUS. We have recently been awarded Oxford Haematology

Biomedical Research Centre (BRC) funding to conduct a feasibility study to trial application of the MGP Panel on MGUS bone marrow specimens. In SECURE, a proportion of MGUS patients are expected to receive bone marrow biopsy as part of their diagnostic workup; a fraction of these patients may progress to SMM or MM with second biopsy samples. Therefore, the prospective nature of SECURE is expected to provide the unique opportunity to collect paired bone marrow specimens. Pending results of our ongoing feasibility studies, it may be of interest to apply the MGP Panel to paired samples of progressors from SECURE in the future. Such study is expected to yield the prognostic value of somatic mutations in MGUS, which may suggest the potential for genomic risk stratification to guide monitoring frequency for MGUS.

SECURE will explore metabolomics as a tool to identify biomarkers of MGUS progression. A growing body of literature have applied metabolomics to the study of plasma cell dyscrasias, highlighting acetyl carnitine as a novel marker of active disease[27], and elevated serum 2-hydroxyglutarate (2-HG) as associated with higher levels of c-MYC expression in MM and a shorter time to progression[28]. More recently we have analysed serial samples obtained in Birmingham from 12 MGUS patients before and after progression to MM and in a second cohort, serial samples from MM patients at diagnosis (before treatment), during treatment and in remission. This preliminary work has identified a number of candidate metabolites; for example, serum sphingosine-1-phosphate (S1P) levels were higher in MGUS individuals prior to their progression to MM ($p<0.05$, mean fold change of 7.5) and this change in S1P levels was progressively reversed during MM therapy and in first remission. In SECURE, we aim to leverage prospective recruitment of MGUS patients who later progress, to analyse serial samples and identify further biomarkers of disease progression using ultra-performance liquid chromatography-mass spectrometry (Ultimate3000 UPLC system coupled to an electrospray ionisation Q Exactive Plus mass spectrometer)[29,30]. This work will be undertaken in the Phenome Centre-Birmingham (PC-B), a £8M facility purposed for large scale targeted and untargeted study of metabolites present in human biofluids and tissues for precision medicine.

The proposed study will understand the value of post-translational modifications (PTMs) of serum free light chains as MGUS biomarkers. Colleagues from the Mayo Clinic have recently shown evidence in support of this, in a screened MGUS cohort[31]. Furthermore, recent work has shown N-linked glycosylation transcriptional programs to be significantly upregulated in plasma cells from patients with AL amyloidosis in comparison to patients with MM and normal controls[32]. Collectively, these studies highlight PTMs of light chains as a candidate marker of MGUS progression. In SECURE, we will leverage a mass spectrometry platform established by binding site to longitudinally profile glycosylation patterns in light chains of MGUS patients, to test the potential of this approach to predict progression to MM or amyloidosis.

Overall, SECURE provides a platform for prospective collection of serial samples, that can help better dissect mechanisms and markers of MGUS progression. We aim to apply genomics to study germline predisposition to development of MGUS, but also to test whether

somatic variants in MGUS could be used to risk stratify progression to MM. Furthermore, we aim to investigate two novel avenues of biomarker discovery for MGUS progression – namely, metabolomics and PTMs of light chains. These intended works utilise existing academic collaborations with institutions that have pioneered their respective technologies.

5.3. Exploring patient and population impact of MGUS diagnosis and follow-up

An unresolved question is the psychological impact of MGUS diagnosis and monitoring. Whilst MGUS is increasingly common in the aging population, present in 3.2% of individuals older than 50 years[3], it is only rarely diagnosed, mostly incidentally, and 80-90% of MM patients are diagnosed without first receiving MGUS diagnosis[33]. This suggests that greater efforts for earlier MGUS diagnosis and monitoring may enable earlier MM diagnosis and treatment, which has been shown to improve outcomes in MM. On the other hand, the absolute risk of progression is still relatively low (1%/year) and studies have highlighted potential psychological distress that comes from MGUS diagnosis. In SECURE, we aim to study the psychological impact of MGUS diagnosis through a patient-centric approach.

Currently, the psychological impact of MGUS diagnosis is poorly understood. Previous work has suggested that of patients referred to haematology services for non-malignant conditions, 46% and 40% experience anxiety and stress, respectively, and 30% fear having cancer during the referrals process[5]. For some patients, MGUS diagnosis invoked social comparison with other cancer patients and increased fears of developing MM, whilst others saw MGUS diagnosis as an opportunity to make positive lifestyle changes[34]. Whilst the harms of overdiagnosis have been extensively studied in solid tumours[35], comparatively little is known about the psychological impact of MGUS diagnosis. With population-wide prospective trials of MGUS screening underway in Iceland (iStopMM study)[36], studying the psychological benefits and harms of MGUS diagnosis is of increasing importance. In SECURE, we aim to understand the prevalence and predictors of patient-reported anxiety and depressive symptoms during diagnosis and longitudinal follow-up of MGUS. Understanding the psychological impact of MGUS is expected to suggest avenues through which to minimise the iatrogenic harm of diagnosis, which will be important on a patient level.

On the population level, we aim to study the population-level wide economical and resource cost of MGUS care. MM has a high economic burden due to costs of hospitalisations and novel therapies[37]; because preceding MGUS diagnosis is linked with improved MM outcomes, MGUS screening may be expected to reduce population costs of MM care. In support of this, computational models suggest that population-wide MGUS screening 6-yearly from the age of 55 years would reduce MM prevalence by 19% and MM-specific mortality by 40%[38], which may translate into reduced cost of healthcare. On the other hand, a recent study estimated the annual healthcare cost of diagnosing and monitoring MGUS as over $100 million in the US, based on an estimated 500,000 individuals living with MGUS and assuming once-yearly follow-up[39]. The cost of MGUS management in the UK is currently unknown, preventing progress in the debate. SECURE will provide a platform to prospectively assess the costs for

a national health service in diagnosing and monitoring MGUS. The results of such work may inform cost-effective MGUS screening efforts in the future.

Overall, the third major aim of SECURE is to take a patient- (and population-) centric approach to understanding the impact of MGUS diagnosis and monitoring. The prospective design of this proposed study will support longitudinal study of psychological impact on the level of individual patients, and the economic impact for the population.

Clinical impact: A factual understanding of progression of Monoclonal gammopathy to Myeloma in a UK population is needed. This study will provide additional information on diagnostic routes, screening for MGCS, monitoring patterns and both psychological impact as well as health resource utilisation of this patient population. This will allow us to risk stratified monitoring of patients with MGUS, and streamline pathways with intent to early diagnosis of MGCS. Additional data on family linkage, QoL and HRU helps develop a framework for enhanced clinical management of MGUS.

6. OBJECTIVES AND OUTCOME MEASURES

6.1. Primary objective

The primary objective of the study is to understand the rate of progression from MGUS to Myeloma.

Primary Objectives	Outcome Measure	Time points of evaluation
Progression rate to MM	Primary: Incidence rate of MM during observation	Baseline and annual follow-up or disease progression by study team

Table 1: Objectives and endpoints including frequency of measurements

6.2. Secondary Objectives

Secondary aims include understanding the routes of identification of MGUS patients, monitoring patterns and how their disease is monitored, incidence of MGCS within this cohort, risk of progression to myeloma in a incidental MGUS diagnosis cohort and their quality of life of MGUS patients including emotional health. In addition, this study will generate data around biomarkers of disease progression.

Secondary Objectives	Outcome measures	Time points of evaluation
To determine the monitoring patterns of patients with	Qualitative analysis:	Baseline and annual follow-up by study team

MGUS and the rationale behind them (Hospital/ GP/ Lab, frequency)	Remote or face to face monitoring by Secondary Care Primary Care based monitoring Direct lab-based monitoring	
Screening for MGCS	Qualitative analysis: Tests/ clinical evaluation for MGCS	Baseline and annually
Understanding routes to MGUS diagnosis (Screening/ Incidental , Secondary/ Primary care)	Qualitative analysis: Screening vs Incidental	Baseline
To understand family linkage in relation to MGUS	First degree family member Second degree Family history No family History	Baseline and annual follow-up by study team
QoL: To use questionnaires to better understand the impact of MGUS diagnosis on QoL post diagnosis (annual)	EORTC QLQ-C30	Annually by members of study team
HRU	EQ5D annually HE analysis with primary care and HES data	Annually. Study investigators will seek GP data from CPRD and HES data
Determine if S1P and acetyl carnitine have value as a predictive biomarker for progression to MM	Correlate their rate of change with progression	Baseline and annual follow-up
Identify new biomarkers to detect early disease progression	Mass spectrometry Genomic profiling	Baseline and annual follow-up
Identify germline genetic variants associated with risk of developing MGUS and/or MM	Germline genetic profiling	Baseline, sample can be taken at later timepoint if missed

Table 2: Secondary Objectives and endpoints including frequency of measurements

7. STUDY DESIGN

7.1. Methodology

This is a longitudinal observational cohort study which will recruit patients within England. Samples taken for this study will be transferred to the HaemBio Biobank at the Weatherall Institute of Molecular Medicine, University of Oxford. Relevant samples will then be distributed to the OUHFT immunology laboratory or the Phenome Centre, University of Birmingham for testing and storage as required. Peripheral blood EDTA samples for germline genetics will be transferred to the Institute of Cancer Research for storage and analysis. Please see Appendix A 17.1 for a schedule of assessments.

Participants will be identified and approached by a healthcare professional that is part of their clinical care team within the haematology department of the hospital they are attending and any standard investigations the treating clinician deems necessary for their diagnostic evaluation within the NHS protocols will be performed. The participants will not have any invasive procedures, outside of standard care, as part of this study.

Any research specific assessments and sampling should coincide with routine clinical appointments wherever possible. Participants will be asked to complete a validated CRF and questionnaire which will be entered onto a secure database.

Where consent is obtained, participants' primary and secondary healthcare data will be compared to a matched population via the Hospital Episode Statistics (HES) dataset to give detailed comparative information regarding heath economics in the study cohort.

7.2. Duration of Study

There is a planned follow up of 60 months. Participant recruitment will begin in September 2022 and end September 2024. The time frame consists of a 24-month enrolment period, with continuous observation. The data collection for the study is due to conclude in September 2029, 5 years after the last participant is recruited. The final analysis of results will take place until September 2030.

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7.3. Expected Outcomes of the Study

1. Identify the risk of progression of MGUS patients diagnosed in routine clinical care
2. Describe the incidence MGCS and the test use for diagnosis in routine clinical care– amyloidosis, bone, renal, neurology and skin, other suspected organs eg myopathies
3. Understand and describe the physical and emotional burden of MGUS
4. HRU helps develop a framework for costs involved in managing MGUS in the community
5. Identification and exploration of new biomarkers to detect early disease progression.

8. PARTICIPANT IDENTIFICATION

8.1. Sample size

The primary objective of the study is to explore whether previously published progression rates of MGUS to MM (1% per annum) is observed in an unselected cohort of patients with monoclonal gammopathy in UK. With 2000 participants and a 5 year follow up with a progression rate of 1% we would expect approximately 100 active myeloma cases by the end of the follow up. With an expected progression rate of 5% over the 5 year follow up and 2000 participants the expected confidence interval around the progression rate would be from 4% to 6% with a precision of ~2% (Table 3).

	Sample size			
Expected Progression rate	1000 participants	1500 participants	2000 participants	2500 participants
2.5% (0.5% per year)	1.9%	1.6%	1.4%	1.2 %
5 % (1% per year)	2.7%	2.2%	1.9%	1.7%
7.5% (1.5% per year)	3.2%	1.3%	2.3%	2.1%

Table 3. Expected confidence intervals

8.2. Study Participants

Participants will be those with a diagnosis of Monoclonal gammopathy as defined in the table below:

	Definition	Progression rate
Non-IgM monoclonal gammopathy of undetermined significance	Serum monoclonal protein (non-IgM type) <30 g/L Clonal bone marrow plasma cells <10%* Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder	1% per year
IgM monoclonal gammopathy of undetermined significance	Serum IgM monoclonal protein <30 g/L Bone marrow lymphoplasmacytic infiltration <10% No evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder	1.5% per year

Light-chain monoclonal gammopathy of undetermined significance	Abnormal FLC ratio (<0·26 or >1·65) Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1·65 and increased λ FLC in patients with ratio <0·26) No immunoglobulin heavy chain expression on immunofixation Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells <10% Urinary monoclonal protein <500 mg/24 h	0.3% per year

Table 4. MGUS classification. Adapted from Rajkumar et al. Lancet Oncol. 2014 Nov;15(12):e538-48

Patients who are suitable for the study will be identified by the treating haemato-oncology clinician, the clinical nurse specialist, the myeloma service coordinators and at the local multidisciplinary team (MDT) meetings in the participating hospitals. Weekly updates between the local PI and the myeloma service coordination team will ensure eligible patients are identified and the process of informed consent is initiated.

Patients are eligible for the study if all the inclusion criteria are met and none of the exclusion criteria applies. Confirmation of eligibility must be documented in the patient's notes and on the Full Registration Case Report Form (CRF).

Patients with MGUS are eligible to be included in the study if they meet the following criteria:

8.3. Inclusion Criteria

- Any individual with a confirmed or suspected case of MGUS

8.4. Exclusion Criteria

- Those who are unable or unwilling to give informed consent
- Patients under the age of 18
- Patients with no evidence of MGUS
- Patients with a light chain ratio of 0.3 to 3.0 without a monoclonal protein on serum electrophoresis or immunofixation
- Patients with rapidly rising paraprotein or serum free light chains of progressive disease at time of diagnosis or inclusion into study

9. STUDY PROCEDURES

9.1. Recruitment

Commented [SS4]: Does this mean we include those who have not had a marrow because there were no suspicious features when first assessed? This is ok since this is current practice, but may present problems with analysis because some SMM pts with >10% pc, but low level, in marrow might have been included. Need to anticipate this

Commented [kR5R4]: Agree has impact on sample size but w ecan review after first year

Commented [BR(O6R4]: Should we add an interim analysis section? Can also look at IgM numbers recruited etc

Commented [kR7R4]: Ask Constantinos if we could have a 6 monthly revie wof profile of mgus patients recruited and sampel size adjusted to improve prediction models

MGUS patients who are eligible will be invited to participate. Patients who fit the criteria will be identified by the treating haemato-oncology clinician, the clinical nurse specialist, the clinical care team, the myeloma service coordinators and/or at the local multidisciplinary team (MDT) meetings at the participating sites. Potential patients will then be approached by an informed member of the myeloma clinical research team during a routine clinic visit or via telephone and the current version of the participant information sheet (PIS) will be provided, via email or post if necessary. If the participant is interested then they will be offered a further detailed discussion about the study with a member of the research team. They will return to clinic after a minimum period of 24 hours, and will have the opportunity to ask any questions regarding the study. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking the consent is satisfied that the patient understands the study and implications. If the participant remains happy to enter the study, their informed consent will be obtained by the investigator prior to initiating any study related investigations.

9.2. Informed Consent

Participants' informed consent will be taken at a routine clinic visit. The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

In addition, patients will be asked if they would allow any surplus material to be stored by HaemBio for use in future ethically approved studies. Patients will also be asked if they are willing to be contacted about future ethically approved studies. These will both be optional and will not affect the patients' participation in the current study. All material will be stored in accordance with the Human Tissue Act 2004.

Consent will also be requested to allow members of the research team to access participants primary and secondary healthcare data in order to study health economics by comparing cohort to matched population via HES database.

Sites are responsible for assessing a patient's capacity to give informed consent. Sites must ensure that all patients have been given the current approved version of the PIS. Sites must assess a patient's ability to understand the verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the study.

The CI, or, where delegated by the CI, other appropriately trained site staff, are required to provide a full explanation of the study. Written and verbal versions of the PIS and Informed

Consent Form (ICF) will be presented to the patient detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The patient will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Informed consent will then be obtained and evidenced by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained consent must be suitably qualified and experienced, whilst having been authorised to do so by the CI/PI. A copy of the signed ICF will be given to the participant. The original signed form will be retained at the study site and a copy should be filed in the medical records.

Those who have not communicated a decision regarding consent may be re-approached on one occasion after 2 months by the local research team.

9.3. Screening and Eligibility Assessment

9.3.1 Screening Logs

The research team will be expected to maintain a screening log of all potential participants. Potential participants will not be registered or consented and therefore during screening, potential participants should be identified by limited information only; this should include MRN/NHS number, initials, date of birth, screening data, confirmation of diagnosis (confirmed jointly by the Haematology and Immunology teams) and outcome of the screening process (e.g. enrolled into study, reason for ineligibility if known, or refused to participate). Screening logs will be stored securely with restricted access.

9.3.2 Screening Assessments

All screening study assessments must be completed before any study procedures are carried out. All laboratory screening assessments will have been carried out prior to recruitment in the study in order to give a formal diagnosis of MGUS.

- **Medical History**
  - Detailed history of MGUS including date of diagnosis. Any co-morbidities should be noted. Any clinical problems from patient history, even if not formally defined as a comorbidity

- **Treatment History and Concomitant Medication(s)**

- Details of treatment history/current treatment/planned treatment should be captured. Concomitant medication, including all medications, treatments and therapies use in the prior 4 weeks, as well as those currently being taken should be recorded.

- **Local Clinical Laboratory Evaluations**
  - Previously carried out as standard care to give a formal diagnosis of MGUS. This will usually include:
    - Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Urea, Creatinine, LFTs, CRP, LDH, Creatinine Clearance (EGFR), proBNP and Troponin.
    - Urine: urine albumin/creatinine ratio, urine/protein creatinine ratio
    - Immunology: paraprotein (type and concentration), quantitative immunoglobulins, sFLC.
    - Haematology: Full blood count to include: white blood cells, neutrophils, lymphocytes, haemoglobin, haematocrit, platelet count.
    - Bone marrow assessment (if performed): Bone marrow aspirate with/without trephine to confirm diagnosis of MM/SMM (not all patients – clinician discretion). Morphological (% bone marrow plasma cells), immunophenotyping and genetic testing (FISH) may be carried out.
    - Imaging (if performed): Whole body imaging as appropriate – Low dose whole body CT, DW WB MRI, FDG PET/CT, MRI whole spine, pelvis, MRI marrow are all acceptable. Occasionally clinical discretion is applied, and imaging is not performed. This is only acceptable for patients without bone pain symptoms.

Commented [UHB8]: Would add proBNP and troponin

Commented [UHB9]: Would add urine for proteinuria - ACR

Commented [BR(O10R9]: Karthik: should this be listed here or separately?

9.3.3 Recruitment Logs

Participants deemed eligible after screening will be registered on to the study and be given a unique Study ID. Registered participants will be recorded on an enrolment log with information including Study ID, date of birth, initials, hospital number and date of consent. No personal information which may identify the participant should be included in the recruitment log.

9.4. Baseline Assessments

Commented [FK(O11]: Make it clear where these are assessments done as part of clinical care.

- **Personal and Family Medical History**
  - Detailed history of MGUS including; date of diagnosis. Detailed description of all prior and on-going diseases and disorders should be documented. Detailed family medical history.
- **Physical Examination**

  - Weight, height and assessment of ECOG performance status.
- **Concomitant Medication** (data from screening assessments may be used)
  - Details of current concomitant medication including all medications, treatments and therapies.
- **Quality of Life and Health Anxiety Questionnaires**
  - Participants will be asked to complete validated quality of life and health anxiety questionnaires.
- **Local Clinical Laboratory evaluations** (data from screening assessments may be used)
  - Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Urea, Creatinine, LFTs, CRP, LDH, Creatinine Clearance (EGFR), proBNP and Troponin.
  - Urine: Urine albumin/creatinine ratio, urine/protein creatinine ratio
  - Immunology: paraprotein (type and concentration), quantitative immunoglobulins, sFLC
  - Haematology: Full blood count to include; white blood cells, neutrophils, lymphocytes, haemoglobin, haematocrit, platelet count.
  - Bone marrow assessment (if performed): Bone marrow aspirate with/without trephine to confirm diagnosis of MM/SMM (not all patients – clinician discretion). Morphological (% bone marrow plasma cells), immunophenotyping and genetic testing (FISH) may be carried out.
- **Imaging** (if performed as standard care)
  - Whole body imaging as appropriate – Low dose whole body CT, DW WB MRI, FDG PET/CT, MRI whole spine, pelvis, MRI marrow are all acceptable. Occasionally clinical discretion is applied, and imaging is not performed. This is only acceptable for patients without bone pain symptoms.
- **Translational Sample collection**
  - 10 ml of sera and 10 ml EDTA to be taken (10 ml EDTA if BM aspirate collected).

Commented [FK(O12]: Make it clear these are part of standard care

9.5. Annual follow-up visits

- **Personal and Family Medical History**
  - Any relevant updates since the last study visit.
- **Physical Examination**
  - Weight and assessment of ECOG performance status.
- **Concomitant Medication**
  - Details of current concomitant medication including all medications, treatments and therapies. This includes any changes since previous study visit.

- **Quality of Life and Health Anxiety Questionnaires**
  - Participants will be asked to complete validated quality of life and health anxiety questionnaires.
- **Local Clinical Laboratory evaluations** (data from standard care should be used)
  - Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Urea, Creatinine, LFTs, CRP, LDH, Creatinine Clearance (EGFR), proBNP and Troponin.
  - Urine: Urine albumin/creatinine ratio, urine/protein creatinine ratio
  - Immunology: Beta-2-microglobulin, paraprotein (type and concentration), quantitative immunoglobulins, sFLC
  - Haematology: Full blood count to include; white blood cells, neutrophils, lymphocytes, haemoglobin, haematocrit, platelet count.
  - Bone marrow assessment (if performed): Bone marrow aspirate with/without trephine to confirm diagnosis of MM/SMM (not all patients – clinician discretion). Morphological (% bone marrow plasma cells), immunophenotyping and genetic testing (FISH) may be carried out.
- **Imaging** (if performed as standard care)
  - New imaging findings if performed e.g. vertebral compression etc
- **Translational Sample collection**
  - 10 ml of sera and 10 ml EDTA to be taken (10 ml EDTA if BM aspirate collected)

Commented [FK(O13]: Make it clear these are part of standard clinical care

9.6. Disease progression visit (as determined by routine clinical care team)

Commented [YK14]: How will you know when patients progress?

Commented [BR(O15R14]: As determined by routine clinical care team

- **Personal and Family Medical History**
  - Any relevant updates since the last study visit.
- **Physical Examination**
  - Weight and assessment of ECOG performance status.
- **Concomitant Medication**
  - Details of current concomitant medication including all medications, treatments and therapies. This includes any changes since previous study visit.
- **Quality of Life and Health Anxiety Questionnaires**
  - Participants will be asked to complete validated quality of life and health anxiety questionnaires.
- **Local Clinical Laboratory evaluations** (data from standard care should be used)
  - Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Urea, Creatinine, LFTs, CRP, LDH, Creatinine Clearance (EGFR), proBNP and Troponin.
  - Urine: Urine albumin/creatinine ratio, urine/protein creatinine ratio.

- Immunology: Beta-2-microglobulin, paraprotein (type and concentration), quantitative immunoglobulins, sFLC.
- Haematology: Full blood count to include; white blood cells, neutrophils, lymphocytes, haemoglobin, haematocrit, platelet count.
- Bone marrow assessment: Bone marrow aspirate with/without trephine to confirm diagnosis of MM/SMM (not all patients – clinician discretion). Morphological (% bone marrow plasma cells), immunophenotyping and genetic testing (FISH) may be carried out.

- **Imaging** (if performed as standard care)
  - New imaging findings e.g. vertebral compression etc
- **Translational Sample collection**
  - 10 ml of sera and 10 ml EDTA to be taken (10 ml EDTA if BM aspirate collected)

Commented [FK(O16]: As above

9.7. Sample Handling

All participants will be assigned a unique Study ID which will also be used to identify samples. All laboratory samples taken specifically for this study will be anonymised by the research team.

Samples taken will follow the separate standard operating procedure (SOP) for transport to the laboratory and subsequent analysis and storage.

All samples taken for the purpose of the study will be stored at the HaemBio Biobank (HTA Licence No. 12433) in the Weatherall Institute of Molecular Medicine which provides restricted access. Access to samples, including but not restricted to the work detailed in this protocol, will then be granted by following the procedures set out by the biobank. Stored samples will only be accessible to study staff and authorised personnel.

Commented [BR(O17]: To be updated when process is clarified

Commented [FK(O18R17]: Has this been updated?

Commented [FK(O19]: There is no mention here of samples going to Birmingham and ICR. Will they be going from the Biobank?

Commented [BR(O20R19]: All samples will go to BioBank initially for storage

The stored samples will be kept for 5 years after the study has ended unless the CI and investigative team decide there is no longer a use for the samples or if the CI leaves the department and there is no successor to securely oversee the sample storage. In this case the samples will be disposed of in accordance with the Human Tissue Authority Code of Practice. Prolonged storage and further use of the samples will all be subject to ethical approval.

9.8. Early Discontinuation/Withdrawal from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of consent
- Loss to follow up

For participants who are withdrawn from the study, identifiable data or samples already collected with valid consent would be retained and used in the study. No further data or samples would be collected or any other research procedures carried out on or in relation to the participant. All withdrawal information including reason for withdrawal will be recorded.

Commented [FK(O21]: Is there a reason this has been taken out?

9.7.1 Participant Transfer

For participants moving from the area, every effort should be made for the participant to be followed-up at another participating study site and for this site to take over responsibility for the participant. If the participant is happy to transfer to another site and continue follow up, the main study contact at the current hospital should liaise with the SECURE study Coordinator to identify a suitable receiving hospital (if possible) and facilitate the transfer.

9.9. Definition of End of Study

The end of study is the date of the last follow up of the last participant. The final follow up for patients will be September 2029. If data collection for the study is to be extended beyond this point then an amendment will be made to the study. Data analysis and final write up is due to end September 2030.

9.10. Study Management

As the lead applicant, the CI (Karthik Ramasamy) will have overall responsibility for the outputs of this research study and will have responsibility for security and access to the data. Prof Guy Pratt, Dr Ross Sadler and Dr Kassim Javaid will contribute to the design of the study. The local hospital PI and the myeloma team will take responsibility for identifying potential study participants. The PI will responsible for ensuring informed consent is given and will also aid in the interpretation of clinical data. The statistician for SECURE study will perform the data analysis. This will be supported by the trial investigators.

9.11. Co-enrolment

Patients may also be enrolled in observational studies and clinical trials for treatment whilst on this study.

Commented [BR(O22]: R&D: This is a non-interventional study that only takes blood samples which has a well known safety profile. Can we therefore remove safety monitoring from the study?

10. SAFETY REPORTING

Due to the observational nature of the study no safety reporting will be performed.

11. STATISTICS AND ANALYSIS

11.1. Description of Statistical Methods

This is an observational study to collate clinical and laboratory parameters that will include protein, genomic and immune function markers on patients with MGUS.

The primary outcome which is the incidence rate of progression to myeloma will be estimated yearly and at the end of the follow up along with 95% confidence intervals.

Descriptive statistics will be used to summarize the dataset overall and by myeloma status at the end of the follow up.

Continuous variables will be summarised with the use of mean (SD) or median (IQR) according to the normality of the distribution and binary/categorical variables will be summarised with the use of proportions.

Analyses will be exploratory with the general aim of identifying associations between parameters which may be beneficial for future research. When examining associations involving time-to-event data, such as time to relapse or time to progression, Kaplan-Meier survival analysis and Cox regression will be used. Continuous measures will be examined using linear regression and binary outcomes using logistic regression. Multivariable analyses may also be performed to control for confounding factors which may obscure associations between parameters.

Commented [CK23]: It is likely that we won't have a big enough sample size in order to robustly do all these analyses. We have to acknowledge this

Commented [BR(O24R23]: Acknowledged in section 15.8

With the Birmingham samples, we will collect full-scan and MS/MS data to provide relative quantification of metabolites and metabolite annotation/ identification. Metabolite annotation/identification will utilise matching to an in-house accurate mass and MS/MS mass spectral library or to publicly available MS/MS mass spectral libraries and databases (e.g. mzCloud). All data will be processed applying Compound Discoverer v3.1 to generate a single data matrix. We will perform statistical analysis followed by a defined filter process to identify the metabolites of highest statistical and biological importance. Specifically, we will remove all metabolites with the exception of those that meet the criteria of (i) false discovery rate (FDR)-corrected p-value > 1×10^{-6}; (ii) Area Under the Receiver Operating Characteristic (AUROC) > 0.75 and (iii) a fold change greater than 1.3 with the concentration higher in subjects who have progressed to MM or WM compared to stable MGUS subjects or vice versa.

Commented [BR(O25]: Constantinos: Could Chris add a bit more detail on how they decided on this p.value (one sentence might is enough).

For ICR samples, germline genetic analyses will be performed towards the end of the study period, to minimise unnecessary waste of resources on patients lost to follow-up or having withdrawn consent. Due to projected substantial changes in genetic analysis technology, up-to-date genetic analyses methods available will be evaluated at the time of planned analysis and the method providing highest information gain for resource available selected, in line with anticipated patient wish for optimal evidence generation.

11.2. Interim analysis

An interim analysis will be undertaken 12 months after the study opens. This analysis will include but not be limited to: a review of the profile of MGUS patients recruited with a sample size adjustment if required to improve prediction models; recruitment rate and analysis of data robustness and completion rates.

Commented [BR(O26]: To be checked

Commented [BR(O27]: Or 6 months?

12. DATA MANAGEMENT

12.1. Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. Where possible, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institutions for monitoring and/or audit of the study to ensure compliance with regulations.

Only authorised personnel involved in the study will be able to access medical records and personal information for the purposes of the study or to inform clinical care. For confidentiality purposes, all participant information outside of the clinical use will be pseudo-anonymised with a unique Study ID used to identify the patient. The research data will be stored on an OpenClinica database accessible on a cloud server using multiple layers of security designed to secure the integrity of the system and data it contains. External collaborators will only be able to access anonymised patient data.

Patient identifiers will be separated from clinical/research data and access restricted as to who is able to link these two sets of data to only investigators on the study team. Electronic transfer of personal data will only use encrypted devices.

12.3. Data Recording and Record Keeping

The study eCRF is the initial data collection instrument for this study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done, the item is not applicable, or the question was not asked an option will be provided to state as such.

All essential documentation and research records which contain personal data will be stored securely in accordance with the applicable regulatory requirements with access to stored information restricted to authorized personnel only. All source document data and gathered clinical and laboratory data will be entered on to a secure study database. All electronic documentation and information will be kept on secured servers. All documents will be version controlled. Essential documents will be archived as soon as practicable after the last patient entered onto the study has had their last follow-up. All archived documents will be stored for a minimum of 5 years after publication in a secure location, and remain under access control of the CI, sponsor and regulatory authorities with an audit trail when relevant material is retrieved.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

Due to the nature of the study a risk assessment is not necessary.

13.2. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Commented [FK(O28]: As above.

13.3. Study Committees

13.3.1 Trial management group

The trial management group (TMG) will meet at least annually and will include the Chief Investigators, Investigators, statistician, data manager and trial coordinator. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial data.

13.3.2 Data management group

The data management group (DMG) will meet as required and will include the Chief Investigator, study data manager and trial coordinator. The role of the group is to ensure that the process of collection, cleaning, and management of subject data is in compliance with the study protocol and that high quality data is collected for analysis.

13.3.3 Trial steering committee

The trial steering committee (TSC) comprising of an independent chair, the Chief Investigator, Trial Coordinator, representative of the Sponsor and at least one other clinician not directly associated with the trial, will remain in place throughout the study.

The TSC will provide advice and oversight on trial management and any trial related issues. The roles and responsibilities of the TSC are outlined in the TSC charter.

The TSC will consider the advice of the DMG and may consider discontinuing the trial if the recruitment rate or data quality are unacceptable. The TSC will meet at least once annually although may meet more frequently to discuss specific issues arising, or in e event of any concerns.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

14.1. Serious Breach

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving Research Ethics Committee (REC) and the relevant NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure this study is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the Good Clinical Practice.

15.3. Approvals

The protocol, informed consent form, participation information sheet and any proposed advertising material will be submitted to an appropriate REC, the HRA and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit once a year throughout the study or on request, an Annual Progress report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

15.5. Participant Confidentiality

The study will be run according to ICH GCP after review by the relevant ethics committee. The study staff will ensure the participants' anonymity is maintained. The participants will be identified only by a participant ID on all study documents and electronic database, with the exception of CRF where initials and DOB may be added and a secure database linking the Study ID to the participants NHS/MRN number. Documents with participant's identifiable information will be filed and stored securely; these will only be accessible to authorised personnel. The study will comply with the Data Protection Act 2018 which requires data to be anonymised as soon as it is practical to do so and that data be processed in a lawful, fair and transparent way.

15.6. Expenses and Benefit

No expenses will be required to be claimed by the participants as no further travel will be required past the usual standard of care.

15.7. Other Ethical Considerations

When researching participants' primary and secondary health data only information pertinent to the study will be collected and analysed.

Blood Sample Collection: Patient's skin will be prepped with an anti-septic wipe, which very rarely can cause a skin reaction. If a patient knows they are allergic to the anti-septic prep, another sterile agent will be used. They will then feel a sharp scratch as the needle is inserted and the blood is drawn up into the sample bottles. It is exceedingly rare for blood tests to be complicated; however bleeding and infection are potential risks that will be minimised as much as possible by monitoring for bleeding after the test, and using sterile equipment and the sterile non-touch technique.

All procedures will be carried out by appropriately trained healthcare professionals.

Any clinically significant incidental findings during the testing of blood samples will be reported to the PI and the PI will then report these to the participant via the GP and/or the appropriate clinician in Haematology.

15.8. Potential problem areas

We might be underpowered to answer certain secondary objectives such as identification of new biomarkers to detect early disease progression due to the relatively small number of myeloma cases that will progress by the end of the study. In those cases, we will conduct an exploratory analysis which will allows us to identify the potential usefulness of some of the biomarkers and these findings can help us design further studies. Another potential problem area could be that some eligible patients are missed during the screening process. Ensuring that the myeloma team have full access to this protocol, participant information sheets and consent forms, and frequent communication from the SECURE study team should help all eligible patients to be identified. Patients may be lost to follow up based on local monitoring pathways, strategies to minimise this will be discussed at TMG.

A potential risk to patients is a breach of confidentiality. The study will be run according to ICH GCP after review by the relevant ethics committee. The study staff will ensure the participants' anonymity is maintained. The study will comply with the Data Protection Act (2018) which requires data to be anonymised as soon as it is practical to do so.

16. FINANCE AND INSURANCE

16.1. Funding

The core study including study set up and coordination and sample biobanking is supported by MRC CARP 3 award (MR/V037439/1) and the CRUK Oxford Cancer Centre. Additional funding is being actively sought to support HRU studies and translational work on biobanked samples.

16.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a person is harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

16.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17. PUBLICATION POLICY

The results will be analysed and published as soon as possible after the close of the study. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the CRUK Cancer Centre, Oxford and MRC. Authorship and other contributors will be determined in accordance with the ICMJE and BMJ guidelines. Individual investigators must undertake not to submit any part of their individual data for publication without prior consent of the CI.

18. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the OUH vests in OUH. The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at OUH unless it is generated in collaboration with Oxford University in which case this is led by the University's technology transfer office, Oxford University Innovations.

19. ARCHIVING

Essential documents will be archived as soon as practicable after the last patient entered onto the study has had their last follow-up. All archived documents will be stored for a

minimum of 5 years after publication in a secure location, and remain under access control of the CI, sponsor and regulatory authorities with an audit trail when relevant material is retrieved.

20. REFERENCES

1. Landgren, O. *et al.* Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: A prospective study. *Blood* **113**, 5412–5417 (2009).
2. Landgren, O. *et al.* Association of Immune Marker Changes with Progression of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma. *JAMA Oncology* **5**, 1293–1301 (2019).
3. Biostatistics, A. D.). *Prevalence of Monoclonal Gammopathy of Undetermined Significance A bs tr ac t. Mayo Clinic* www.nejm.org.
4. Kyle, R. A. *et al.* Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia* vol. 24 1121–1127 (2010).
5. Go, R. S. & Rajkumar, S. V. *How I manage monoclonal gammopathy of undetermined significance*. http://ashpublications.org/blood/article-pdf/131/2/163/1406082/blood807560.pdf (2018).
6. Go, R. S., Heien, H. C., Sangaralingham, L. R., Habermann, E. B. & Shah, N. D. Monoclonal Gammopathy of Undetermined Significance: Follow-up Patterns in the United States and Concordance With Clinical Practice Guidelines. *Mayo Clinic proceedings. Innovations, quality & outcomes* **1**, 161–169 (2017).
7. Landgren, O. *et al.* Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. *Blood* **116**, 1056–1059 (2010).
8. Thordardottir, M. *et al.* Obesity and risk of monoclonal gammopathy of undetermined significance and progression to multiple myeloma: A population-based study. *Blood Advances* **1**, 2186–2192 (2017).
9. Landgren, O. *et al.* Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. (2006) doi:10.1182/blood-2005.
10. Wadhera, R. K. & Rajkumar, S. V. Prevalence of monoclonal gammopathy of undetermined significance: A systematic review. *Mayo Clinic Proceedings* vol. 85 933–942 (2010).
11. Castaneda-Avila, M. A., Ulbricht, C. M. & Epstein, M. M. Risk factors for monoclonal gammopathy of undetermined significance: a systematic review. *Annals of Hematology* vol. 100 855–863 (2021).
12. Brown, L. M., Gridley, G., Check, D. & Landgren, O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. doi:10.1182/blood-2007-10.

13. Gregersen, H. *et al. Mortality and causes of death in patients with monoclonal gammopathy of undetermined significance*. *British Journal of Haematology* vol. 112 (2001).

14. Agarwal, G. *et al.* Multiple myeloma screening within a fracture liaison service (FLS). *Osteoporosis International* (2021) doi:10.1007/s00198-021-06233-6.

15. Go, R. S., Gundrum, J. D. & Neuner, J. M. Determining the clinical significance of monoclonal gammopathy of undetermined significance: A SEER-medicare population analysis. *Clinical Lymphoma, Myeloma and Leukemia* **15**, 177-186.e4 (2015).

16. Sigurdardottir, E. E. *et al.* The role of diagnosis and clinical follow-up of monoclonal gammopathy of undetermined significance on survival in multiple myeloma. *JAMA Oncology* **1**, 168–174 (2015).

17. Doyle, L. M. *et al.* Determining Why and Which Clinicians Order Serum Protein Electrophoresis (SPEP), Subsequent Diagnoses Based On Indications, and Clinical Significance of Routine Follow-up: a Study of Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS). *Blood* **114**, 4883–4883 (2009).

18. Rajkumar, S. V. *et al.* Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* **106**, 812–817 (2005).

19. van Nieuwenhuijzen, N., Spaan, I., Raymakers, R. & Peperzak, V. From MGUS to multiple myeloma, a paradigm for clonal evolution of premalignant cells. *Cancer Research* vol. 78 2449–2456 (2018).

20. Vachon, C. M. *et al.* Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. (2009) doi:10.1182/blood-2008-12.

21. Thomsen, H. *et al.* Genome-wide association study of monoclonal gammopathy of unknown significance (MGUS): comparison with multiple myeloma. *Leukemia* vol. 33 1817–1821 (2019).

22. Went, M. *et al.* Identification of multiple risk loci and regulatory mechanisms influencing susceptibility to multiple myeloma. *Nature Communications* **9**, (2018).

23. Kessler, M. D. *et al.* Exome sequencing of 628,388 individuals identifies common and rare variant associations with clonal hematopoiesis phenotypes. doi:10.1101/2021.12.29.21268342.

24. Bick, A. G. *et al.* Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature* **586**, 763–768 (2020).

25. Ajore, R. *et al.* Functional dissection of inherited non-coding variation influencing multiple myeloma risk. *Nature Communications* **13**, (2022).

26. Oben, B. *et al.* Whole-genome sequencing reveals progressive versus stable myeloma precursor conditions as two distinct entities. *Nature Communications* **12**, (2021).

27. Lodi, A. *et al.* Proton NMR-Based Metabolite Analyses of Archived Serial Paired Serum and Urine Samples from Myeloma Patients at Different Stages of Disease Activity Identifies Acetylcarnitine as a Novel Marker of Active Disease. *PLoS ONE* **8**, (2013).

28. Gonsalves, W. I. *et al.* Glutamine-derived 2-hydroxyglutarate is associated with disease progression in plasma cell malignancies. *JCI insight* **3**, (2018).

29. Dunn, W. B. *et al.* Procedures for large-scale metabolic profiling of serum and plasma using gas chromatography and liquid chromatography coupled to mass spectrometry. *Nature Protocols* **6**, 1060–1083 (2011).

30. Dona, A. C. *et al.* Precision high-throughput proton NMR spectroscopy of human urine, serum, and plasma for large-scale metabolic phenotyping. *Analytical Chemistry* **86**, 9887–9894 (2014).

31. Dispenzieri, A. *et al.* N-glycosylation of monoclonal light chains on routine MASS-FIX testing is a risk factor for MGUS progression. *Leukemia* **34**, 2749–2753 (2020).

32. Alameda, D. *et al. Brief Report LYMPHOID NEOPLASIA CME Article Tumor cells in light-chain amyloidosis and myeloma show distinct transcriptional rewiring of normal plasma cell development*. http://www.medscape.org/journal/blood; (2021).

33. Therneau, T. M. *et al.* Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. *Mayo Clinic Proceedings* **87**, 1071–1079 (2012).

34. Murphy, B. *et al.* Patient's perspectives of living with a precancerous condition: Monoclonal gammopathy of undetermined significance (MGUS). *European Journal of Oncology Nursing* **51**, (2021).

35. Welch, H. G. & Fisher, E. S. Income and Cancer Overdiagnosis — When Too Much Care Is Harmful. *New England Journal of Medicine* **376**, 2208–2209 (2017).

36. Rögnvaldsson, S. *et al.* Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. *Blood Cancer Journal* **11**, (2021).

37. Fonseca, R. *et al.* Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia* **31**, 1915–1921 (2017).

38. *Computational Model of Progression to Multiple Myeloma Identifies Optimum Screening Strategies*. (2018).

39. Go, R. S., Swanson, K. M., Sangaralingham, L. R., Habermann, E. B. & Shah, N. D. Clinical prevalence (diagnosed cases) of monoclonal gammopathy of undetermined significance in the US: Estimating the burden on health care. Leukemia vol. 30 1443–1446 (2016).

21. APPENDICES

21.1. Appendix A: Schedule of Assessments

Assessment		First Study Visit	Annual follow-up	Disease progression[c]
Informed consent		x		
Demographics and History		x	x	x
Clinical and Physical Assessment		x	x	x
ECOG performance status		x	x	x
Height and weight		x	x	x
Screening CRF		x		
Monitoring CRF		x	x	x
MGCS CRF		x	x	x
Psychological well-being CRF		x	x	x
Quality of Life Questionnaires		x	x	x
Local clinical Laboratory evaluations[a]	Biochemistry	x	x	x
	Urine			
	Immunology			
	Haematology			
	Bone marrow[d]			
Whole-body Imaging[d]		x	x	x
Translational Samples[b]		x	x	x
Concomitant Medications		x	x	x
Clinically Significant Events			x	x
Standard of care assessments at which disease progression diagnosed				x

[a]Local clinical laboratory evaluations required are itemised in section 9.4.

[b]Translational sample requirements detailed in section 9.

[c]Participants investigated for possible progression but found not to have progressed should continue the protocol scheduled follow-up visits.

[d]At clinicians' discretion. See section 9.

21.2. Appendix B: Amendment History

Amendment No.	Protocol Version No.	Date Issued	Author(s) of changes	Details of changes made