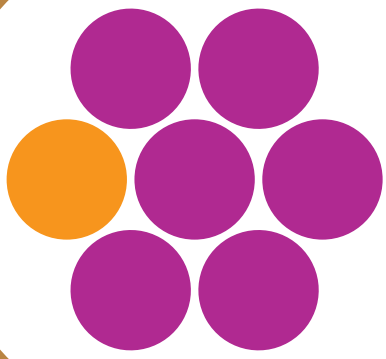
The Rory Morrison Registry



WMUK

First UK Waldenström's Macroglobulinaemia Registry Report

2018

Prepared by

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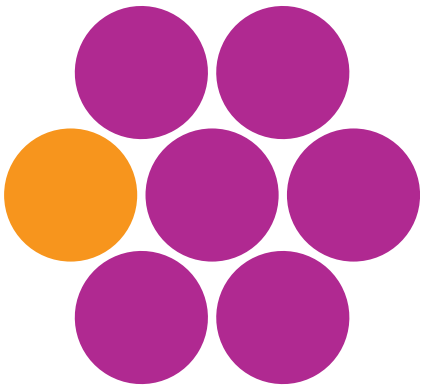

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WMUK operates the The Rory Morrison Registry in partnership with Dendrite Clinical Systems Limited. They gratefully acknowledge the assistance of Dendrite Clinical Systems for:

- building, maintaining & hosting the web registry
- data analysis and
- publishing this report

Dendrite Clinical Systems Ltd maintains the following United Kingdom and GDPR compliant Information Governance and Data Security Certificates:

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- NHS Information Governance Toolkit
- Cyber Essentials
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Ode to a WM patient

So the 'watching and waiting' has come to an end
The treatment's begun and on this the future depends

At clinic the concern is what we might hear
But the way I feel suggests there's nothing to fear
'What do the bloods show!' we almost gasp
You just hope the anxiety will this time pass

Fear of infections is never far away
You just try to forget it and live for the day
A two-year-old grandson and maybe another one
Deserve a grandad with whom a favourite song can be sung
As time goes on you learn more to cope
But it's your nearest who feel it more keenly and end up living in hope.

Tom Miller OBE

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Introduction

Waldenström's macroglobulinaemia (WM) is a rare form of low-grade non-Hodgkin's lymphoma defined by so-called *lymphoplasmacytic lymphoma* (LPL) in the bone marrow alongside an IgM *monoclonal* or *paraprotein* in most cases. WM has an annual incidence in the United Kingdom of approximately 350 new cases *per* year and an estimated prevalence to be around two to three thousand.

WM can present with a vast array of symptoms including lymphoma-related problems such as anaemia, immune deficiency and gland enlargement. The paraprotein can cause high blood viscosity, bleeding problems and a range of immune derangements. Patients may also be asymptomatic.

In order to capture the United Kingdom picture of WM and its diverse complications, disease characteristics, prescribing habits and clinical outcomes, an online registry was developed using generous funds raised by donations to the WMUK Charity.

A consortium of clinicians and patients developed a comprehensive list of important data items, secured ethical approval and established a dedicated review committee to ensure high quality data entry and compliance with data protection laws.

To capture all-comers across the United Kingdom, including less internet-aware / engaged patients, approval was obtained from the National Health Service's (NHS) Confidentiality Advisory Group and Research Ethics Committee to enter anonymised data without patient consent. The approval was future-proofed for the introduction of the EU's General Data Protection Regulation (GDPR) in May 2018 and includes a robust *opt out* mechanism, Fair Processing and Privacy Notices.

The objectives of this Registry are straightforward: to help fulfil the remit of the WMUK Charity of high-quality care and more equitable access to therapies for all patients affected by WM. The most vital tool in such an endeavour is accurate information. This First Report provides an introduction to the power of such information, when captured intelligently and widely.

A crucial part of the Registry is understanding the experience of living with WM and how it feels to receive various treatments. This is especially important in the era of novel therapies which offer a step-change in treating cancer using oral treatments for as long as they are effective. Prospective capture of patient experience is under way with the aim of collecting data for regulators and commissioners as they grapple with funding requests for these effective but expensive drugs.

Patients and clinicians sat side by side at the WM Congress at the Royal Society of Medicine, in London, 1st July 2018

We are immensely grateful to the patients and families whose donations have made this Registry possible and to colleagues in the WMUK National Network for their valuable contributions. WMUK as a charity have provided immense support to patients and their families across the United Kingdom who deal with WM on a *day-to-day* basis.

The Registry is a true collaborative effort between clinicians and patients with the overriding aim of providing a better understanding of WM in the United Kingdom. This makes the United Kingdom an attractive place to trial novel therapies, encourage research into WM and develop new strategies that will improve the management and quality of life for patients with WM.

We hope that our experience of working through the Registry set up, optimisation and regulatory processes can act as an exemplar for other groups who face similar challenges, both in the United Kingdom and beyond.

Dr Shirley D'Sa

Chief Investigator & Data Guardian, RMR

Mr Roger Brown

Chairman, WMUK

A word about Rory

Rory and I became good friends while working together as newsreaders for BBC Radio 4 over 20 years ago. He had a very good sense of humour, was always equable and cheerful and was excellent at his job. I always looked forward to seeing him, because I knew laughter would never be far away.

When he got ill he faced the illness with the same equanimity and humour. We talked about WM a lot together and I was enormously impressed by his attitude and fighting spirit. I know that he would be heartened by the success of the Rory Morrison Registry, and would be fully supportive of any initiative that will enable us to learn more about and better understand WM.

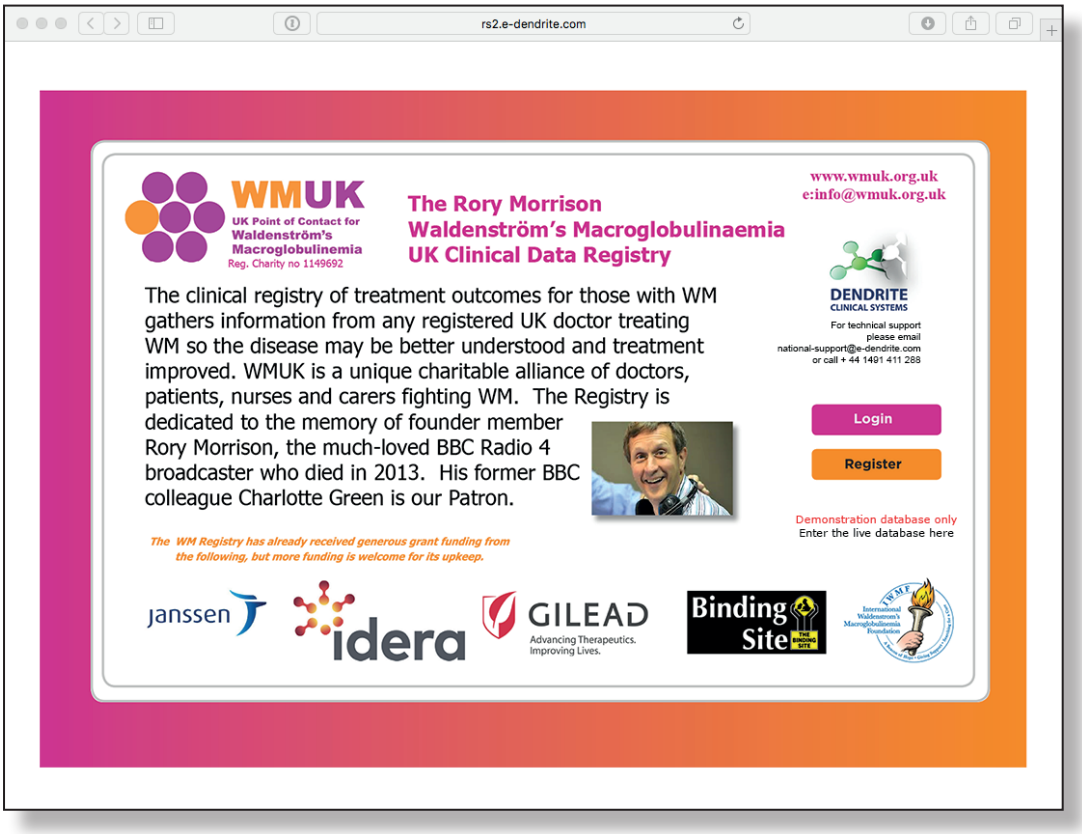
It's a privilege for me to be involved with WMUK and to help keep Rory's memory alive. He was a fine man and I was proud to be his friend.

Charlotte Green

Patron WMUK

Rory Morrison

The home screen of the Rory Morrison Registry



A patient's view of the Registry

I was diagnosed with Waldenström's Macroglobulinaemia (WM) 19 years ago and have had a lot of treatment over the years.

When I was first diagnosed with this rare disease is was very difficult to find information and to understand how it should be treated. There was patchy information mostly gleaned from other blood cancers and thinking amongst doctors that many WM patients are elderly, so the disease is in some way unimportant. We now know that younger people can develop WM too and attitudes are changing, but there is still so much to understand. Around the country there are still differences in how the condition is managed and the information available to patients.

For the first time, thanks to this Registry, we are gathering data on WM in the United Kingdom and what it means to be a WM patient, which will help guide healthcare professionals in caring for their patients. My hope is that it will also help patients to be better informed and to take control of their health.

The Registry is an important source of information on treatments, including those recently approved or in clinical trials. For those facing the challenges of treatment, this is vital as it helps us to understand the options and likely outcomes.

The more data we collect, the more we will understand, so if you are reading this as a doctor seeing WM patients, please participate in the Registry. If you are a patient, please take part in the Patient Reported Outcome surveys and ask your doctor to sign up to the Registry.

Harriet Scorer MB BS FFPM

Patient Trustee WMUK & Member Rory Morrison Registry Review Committee

Executive summary

Overview

- Waldenström's Macroglobulinaemia (WM) is a rare form of lymphoma with a distinct heterogeneity in presenting symptoms, treatment choices and outcomes.
- In recent years, WM has experienced an explosion of novel therapies including oral immunotherapies such as the BTK inhibitors that are radically different in administration and side effect profile to conventional chemotherapies.
- To appreciate the impact of these newer treatments as well as truly understanding the landscape of WM in the United Kingdom, a registry was developed to capture this information.
- Named after Rory Morrison, the beloved BBC presenter and WM patient, the Rory Morrison Registry has been developed to capture this data and we present the first report six months after its national roll out.

Data in the Registry

- In total 579 patients are currently registered from 19 hospitals; this includes 8 patients who have specifically signed up to the Patient Reported Outcomes extension despite their hospital not yet being registered with the Registry.
- In total 11 centres are formally registered, with 5 centres undergoing registration at present.
- Only 6 centres have regularly entered data; the remaining centres have been hampered by delays in local processing and resource allocation.

Demographics and diagnosis

- Traditionally, WM is perceived as a condition of elderly, Caucasian males. Findings from the Registry would suggest that there is a very significant younger population developing WM: over 35% were diagnosed in their thirties, forties or fifties. Similarly, the ratio of male patients : female patients was closer to 1.6 : 1 suggesting a very significant female population with WM or IgM associated condition.
- 51% of patients presented with symptoms of WM relating to paraprotein production (peripheral neuropathy, hyperviscosity or haemolytic anaemia) or lymphomatous related conditions such as anaemia, lymphadenopathy or B symptoms (fevers, night sweats and weigh loss)
- The remaining 49% entered the active monitoring programme (watch and wait) in which a patient usually remains until symptoms develop and treatment is required.

Treatment

- Symptoms are the key indicator to initiating treatment, and the Registry gives us an indication of the variety of symptoms warranting treatment. The patients can roughly be split into three groups: those solely with paraprotein associated symptoms, those solely with lymphoma symptoms and those with a combination of both.
- The time from diagnosis to requiring treatment varies hugely (median 4 months), with some patients remaining on active surveillance for many months or years.
- Most strikingly is the variety of treatments (over 26) used as first line therapy and how these have changed with time. In the past 5 years, we have clearly seen the rise of DRC and R-Bendamustine as the favoured options for first line therapy and the shift away from R-CHOP and Chlorambucil.
- From the Registry, we see most WM patients (over 90%) respond to first line therapy and re-enter active surveillance. This can be for a variable length of time and with the advent of BTK inhibitors licensed in the United Kingdom and the availability of clinical trials treatment options for relapsed disease are even more variable.
- 18% of patient have received or are currently receiving a BTK inhibitor as second line treatment, demonstrating a clear shift away from conventional chemotherapy as second line therapy.

Outcomes

- Based on the Registry, median overall survival in patients presenting with symptomatic WM is 18.5 years and even longer in asymptomatic patients.
- This needs to be taken in the context of the data limitations, but would suggest a promising outcome for patients with WM, even for those who present symptomatically.
- Complications from WM such as high grade transformation have been noted in the analysis, but other complications, for example recurrent infections or treatment complications, will form part of a more comprehensive analysis of the Registry in the future.

Patient Reported Outcomes

- Patient Reported Outcomes (PRO), focussing on symptomatology, quality of life, mental health and disease perception, form a critical part in understanding WM and highlight the need for patients to develop coping mechanisms to deal with this chronic condition.
- We provide an example of the PRO data we collected through the PRO email system or data collected in the outpatient clinic.
- The Hospital Anxiety and Depression Score, a validated tool for assessing anxiety and depression, demonstrates that between 10% and 20% of patients, irrespective of time from diagnosis, could be dealing with anxiety.

The Future

- Planned expansion of the Rory Morrison Registry is currently underway to increase the number of centres registered and patients registered for the PRO extension.
- Continued updates to the Registry include capturing treatment complications and the role of supportive care.
- With further data entry and patient/centre registration the Registry will be used as a hypothesis generating tool alongside its surveillance and observational capabilities.

Conclusions

- The Rory Morrison Registry First Report gives a flavour of WM in the United Kingdom, and the potential a registry has to delve in the intricacies of WM in the United Kingdom.
- It highlights the heterogeneity in WM patients as well as the changing and varied treatment approaches over time.
- Outcome data such as response is subject to significant bias at present, but with the expansion of the Registry in terms of both patients registered and centres registered, this bias will be reduced.
- In summary, the Registry is still in its infancy, but this first report demonstrates the potential of a the Rory Morrison Registry to truly capture the *real world data* and understand the landscape of WM in the United Kingdom for the benefit of patients.

Background

Waldenström's macroglobulinaemia

Waldenström's macroglobulinaemia (WM) is a rare form of low-grade non-Hodgkin's lymphoma defined by >10% involvement with lymphoplasmacytic lymphoma (LPL) in the bone marrow together with an IgM paraprotein [1]. WM has an age standardized annual incidence in the United Kingdom of 0.55 *per* 100,000 that equates to approximately 350 new cases *per* year [2].

WM remains an incurable disease with diverse clinical features and variable outcome. Clinical manifestations of WM can be divided into lymphoma-related (secondary to tissue infiltration) and paraprotein-related. The IgM paraprotein can lead to symptomatic hyperviscosity, secondary AL amyloidosis in addition to a wide spectrum of autoimmune complications such as cold autoimmune haemolytic anaemia, cryoglobulinaemia, and demyelinating neuropathy [2].

The median survival has varied in studies from 5 years to nearly 11 years. The main causes of death due to WM include disease progression, transformation to high-grade lymphoma or complications of therapy. However, owing to the advanced age of these patients, many succumb to unrelated causes [3]. The mortality of asymptomatic patients is similar to that of the general population, whereas it is significantly higher in symptomatic patients who require treatment for WM [4].

Current treatment and novel therapies

The decision to switch from surveillance to treatment remains a complex one given the choice between more aggressive therapy vs avoidance of therapy-related complications and preservation of quality of life [5].

Once the decision to treat has been made, multiple factors including age, patients comorbidities and performance score, disease burden, symptomatology and patient preference come into play. Conventionally first line treatment has taken the form of Rituximab plus chemotherapy, for example Bendamustine [6] ± steroid. More recently, immunotherapies such as ibrutinib in combination or as a monotherapy [7] have been used in front line therapy.

Although incurable, WM is generally a responsive condition with a variable progression free survival and time to next treatment. Therapy in the relapsed setting can include autologous stem cell transplant, novel immunotherapies or conventional chemotherapy. Alternatively patients eligible for a clinical trial will potentially be exposed to pioneering treatments otherwise unavailable. Clinical trials play a critical role in developing optimum treatment regimens and assessing efficacy of novel therapies as well as providing treatment options for patients who have progressed through multiple lines of therapy.

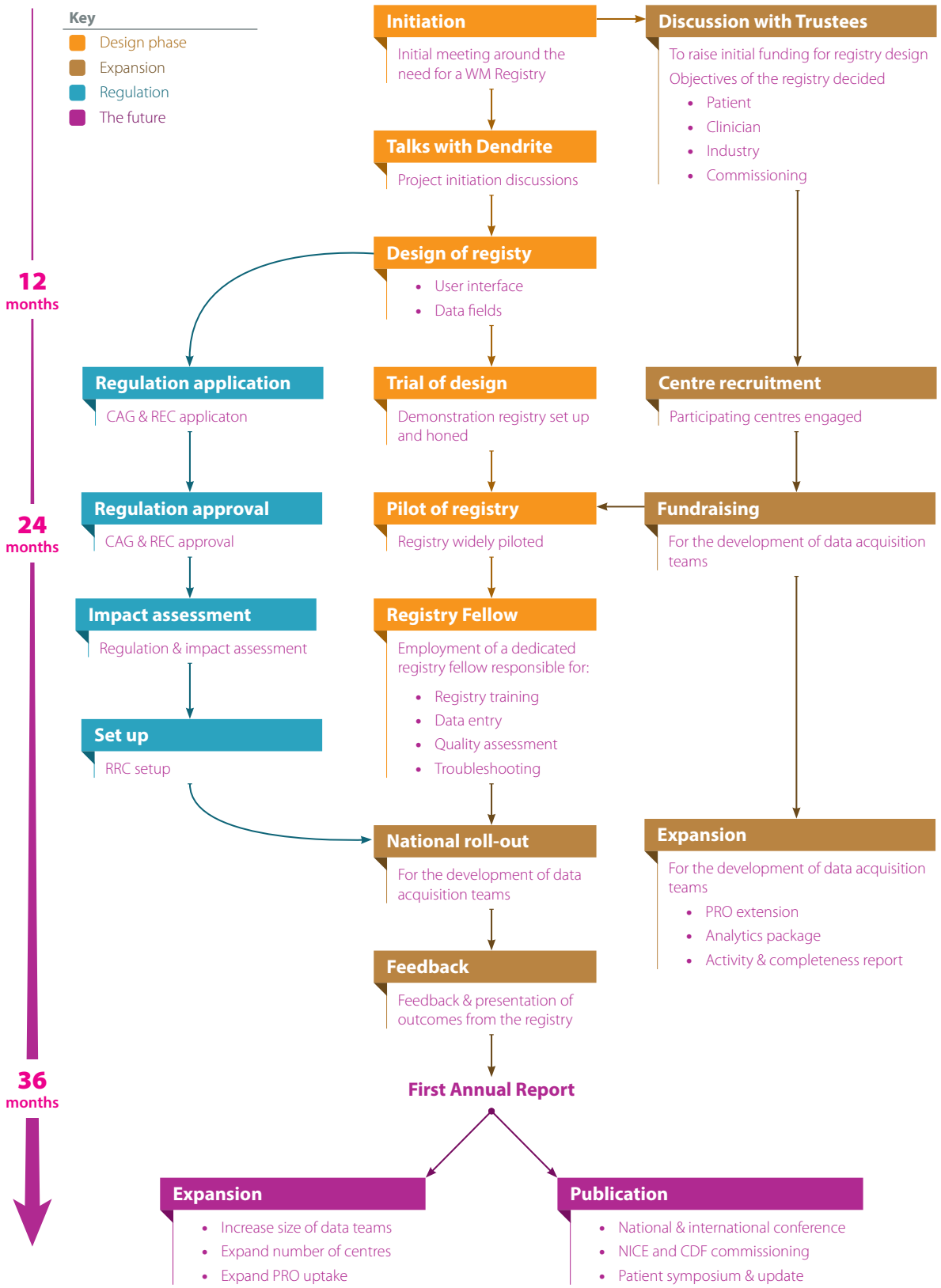
In November 2017, the Cancer Drug Fund (CDF) commissioned ibrutinib, a novel BTK inhibitor, for use in relapsed WM. Ibrutinib, an oral immunotherapy, has a very different side effect profile, tolerability and pharmacology to conventional chemotherapy. Data from the Rory Morrison Registry, with its PRO extension will form part of the reapplication process for ibrutinib to be commissioned by NICE.

The need for a registry

In order to understand the United Kingdom perspective on WM, to contribute to the global effort to improve clinical outcomes, and to work with funding authorities and the pharmaceutical industry towards more equitable access to novel therapies, there is an urgent need to collect real world data on United Kingdom patients affected by WM and related conditions. Accurate demographic and clinical data, robust information around biomarkers, treatment options and patient-related outcomes (PROs) will facilitate the design and entry of United Kingdom patients into clinical trials and demonstrate the clinical value of drugs considered for adoption by the CDF and National Institute for Health and Care Excellence (NICE) within the NHS.

1. Owen, et al. 2003
2. Owen, et al. 2014
3. Morel, et al. 2009
4. Kastritis, *et al.* 2015
5. Dimopoulos, *et al.* 2014
6. Gertz 2018
7. Treon, *et al.* 2018

Registry development timeline



Registry regulation

Research Ethics Committee

An application to the Research Ethics Committee (REC) was made on the 8th September 2017. Application 17/LOLOL/1666 (IRAS222521) was granted a favourable approval on the 20th November 2017 for 5 years duration.

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through Integrated Research Application System (IRAS) are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Confidentiality Advisory Group

WM is managed across the United Kingdom in a combination of district general hospitals and tertiary centres / teaching hospitals. Patients are managed by a variety of haematology teams with differing speciality interests including lymphoma, myeloma or general haematology. This heterogeneity, alongside the infrequency of patients' reviews, meant that consenting patients, especially in non-specialist centres, would prove to be impractical and a critical, meaningful mass of patients on the Registry would not be reached. Therefore approval for data upload without consent under Regulation 5 of the Health Service Regulations 2002 was sought *via* the Confidentiality Advisory Group (CAG) of the Health Research Authority for England and Wales. Separate arrangements are in place in Scotland and Northern Ireland, and this will be addressed in the next phase of the project.

An application to CAG was made on the 30th May 2017. Application 17/CAG/0107 was granted conditional approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent on the 22nd November 2017. There is a robust opt out mechanism for patients to withdraw from the Registry; currently no patient has withdrawn.

General Data Protection Regulation and Data Protection Act

On May 25th 2018 the General Data Protection Regulation (GDPR) was enacted to harmonise data privacy laws across Europe, to protect and empower all EU citizens' data privacy and to reshape the way organizations across the region approach data privacy. To comply with GDPR privacy and fair processing notices as well as subject access. Requests can be located at:

- https://hscn.e-dendrite.com/csp/wm/frontpages/index.html.

Further information for patients regarding the Rory Morrison Registry can be found at:

- https://www.wmuk.org.uk/Rory_Morrison_registry_Project2.

Data sharing and processing agreement

A Data Processing Agreement (DPA) was set up between University College London Hospital as named Data Controllers, and Dendrite Clinical Systems as named Data Processors. A Data Sharing Agreement (DSA) was set up between each contributing centre and UCLH. This allows data to be shared, *via* the Registry platform, and viewed by the administrating team based at UCLH for the purpose of data quality assessment and verification. The DSA and DPA were ratified and signed by the UCLH Information Governance teams.

Registry Review Committee

A Registry review committee (RRC) was created to oversee regulation and data processing. The committee consists of members from Dendrite, WMUK and UCLH. The RRC meet quarterly and their role includes ensuring compliance with regulation and legislation, data quality assessment, troubleshooting and strategy planning.

Registry mechanics

Registry access

The WMUK Registry applications are hosted on secure N3 servers (Carelink) with access from the internet and the NHS N3 network using Internet browsers and authenticated user accounts and passwords. Clinicians and database administrators only have access to the Registry *via* an internet browser using authenticated usernames and passwords. Each user account profile ensures that the users will only view patient records associated with their hospital.

Dendrite has direct access to these servers and the database using secure virtual private network (VPN) connections from their two offices in the United Kingdom, and three senior members of staff from their offices at home. Access is restricted to staff that directly support or manage the database application. All access to the server is logged and audited using best practice guidelines.

Registry security

The Dendrite services are hosted within the Telehouse data centre in London. This is a tier 4 data centre which meets the highest levels of building security including constant security by trained security staff 24/7, electronic access management, proximity access control systems and CCTV. The service platform is held within a secure enclosed suite (TFM20) where access requests are managed *via* the Piksel Service Desk and restricted to Piksel engineers and trusted 3rd party support. Piksel managed CCTV is also installed within the suite and managed 24/7.

Hardened base Operating System images are created as templates to ensure all virtual machines are created with a known baseline level of security and the images are incorporated within our patching policy. Planned monthly maintenance schedule is centred around the release of patches. Patches are released on the 2nd Tuesday of every month and reviewed by the operations team before issuing email notification of when servers will be patched (during the 3rd week of the month), where they are patched automatically, rebooted and tested on each occasion. All servers have Forefront Endpoint Protection AV installed and are configured to use real-time scanning on all file-systems specific file types excluded (e.g, db & log files).

Service delivery and information governance complies with ISO 20000 & ISO 9001 accreditation and the security structure is aligned alongside ISO27001 for continuous assurance and compliance. Internal audits are completed approximately every 3 months and external audits every 6 months.

Registry users

There are three levels of user:

- **Super Administrator** restricted to the Registry Fellow and Dendrite personnel and for the purpose of creating and administering other users accounts:
- **Administrator** the Principal Investigator at each site has Administrator status for their site. They are able to assign rights to Standard Users that allow those users to see demographics for their patients, but cannot set those permissions for their own account(s). Administrators will be able to enter data into registries. Administrators will have the ability to export data extracts for all data in all registries, but such extracts do not contain any patient identifiable data.
- **Standard User** a Standard User is one who is associated with a specific site (or sites) and can enter data into registries. The set of registries visible to Standard Users is be limited by permission setting. Standard Users can create new patients, but only for a site with which they are associated. The ability to create new patients (or to edit the demographics of existing patients) can be controlled if necessary on a user-by-user basis. Standard Users have the ability to export data extracts only for those registries for which they have permission to enter data (restriction is by assigned hospital). These extracts could contain selected patient demographic data from the patient table.

Contributors

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- Shirley D'Sa
- Hanna Renshaw

WMUK

- Roger Brown
- Harriet Scorer

Map demonstrating location of centres currently registered

Analysis

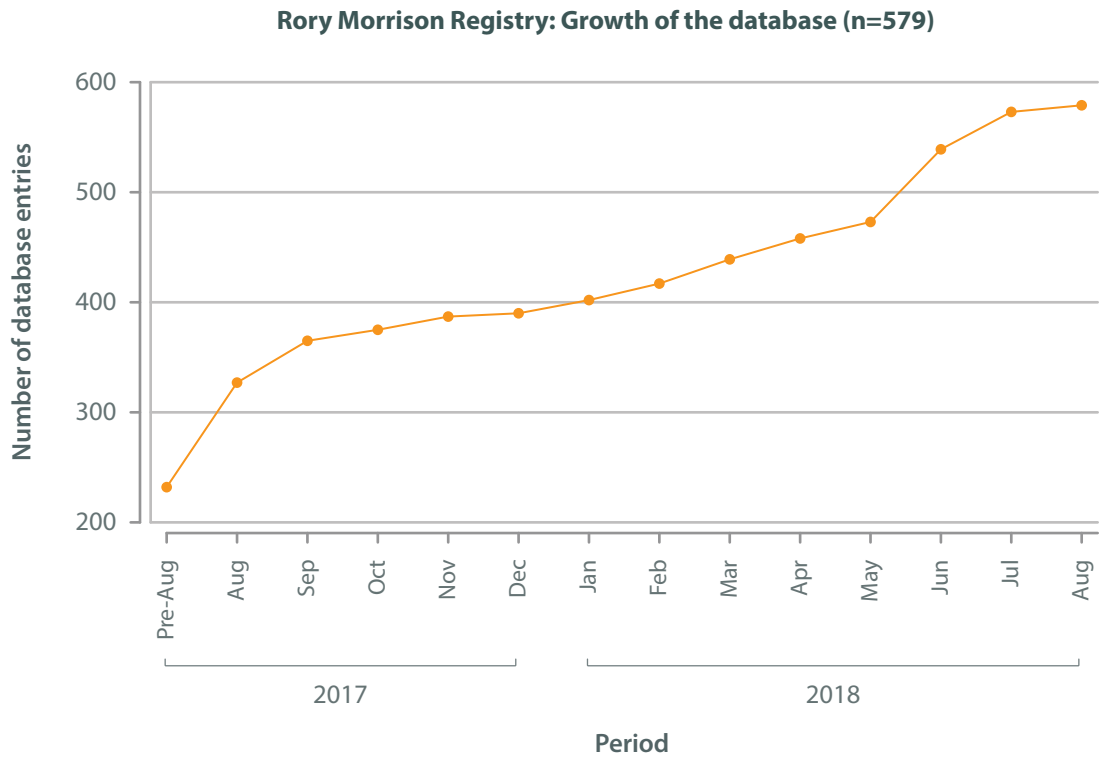
Data in the Registry

The table opposite shows where the patients were seen and which hospitals have been entering data. The majority of information is from 7 centres, and there is a clear skew toward 4 major centres: University College Hospital London, Royal Bournemouth Hospital, Queen Elizabeth Hospital Birmingham and Churchill Hospital Oxford.

Patients who have signed up for the Patient Reported Outcomes (PRO) extension have been registered under their local centre to demonstrate the extent of WM across the United Kingdom. However, if the centre is not yet formally registered with the Rory Morrison Registry, for example Addenbrooke's hospital Cambridge, then no clinical data including the year of diagnosis is included.

For those registered centres, we can see that the date of diagnosis could stretch back over twenty years. This clearly demonstrates the chronic nature of WM and how far reaching the Registry goes.

The graph demonstrates the accrual rate of the Registry. Since the national roll out in January 2018, 179 patients have been added with an average addition of thirty patients registered *per* month. This includes both retrospective and prospective *i.e.,* new diagnosis patient entered. We hope this accrual rate will increase exponentially over the next two years with the expansion of centres inputting retrospective data. Once retrospective data is completed and the use of the Registry has become integrated into clinical practice, the accrual rate will plateau to be in keeping with the incidence of WM in the United Kingdom.



1. In the period August 2017 - July 2018

The Rory Morrison Registry: patients registered per hospital

Hospital	Patients registered	Months data added[1]	Year of diagnosis	
			Earliest	Latest
Addenbrooke's Hospital, Cambridge	1	1	Not recorded	
Belfast City Hospital	1	1	Not recorded	
Chesterfield Royal Hospital	1	1	Not recorded	
Churchill Hospital, Oxford	22	5	2007	2018
Hammersmith Hospital, London	2	1	Not recorded	
Kent and Canterbury Hospital	9	2	2010	2018
Mount Vernon Hospital, Middlesex	1	1	2012	2012
National Hospital for Neurology & Neurosurgery	7	2	2005	2017
Nevill Hall Hospital, Abergavenny, Wales	1	1	2012	2012
Northwick Park Hospital	1	1	Not recorded	
Queen Elizabeth Hospital, Birmingham	26	4	2007	2017
Royal Bournemouth General Hospital	75	3	1996	2018
Royal Devon and Exeter Hospital	2	1	Not recorded	
Royal Marsden Hospital, London	2	1	2004	2013
Royal United Hospital, Bath	2	1	Not recorded	
St James's University Hospital, Leeds	7	2	2009	2014
Stoke Mandeville Hospital, Aylesbury	1	1	2018	2018
Torbay Hospital, Torquay	9	2	2008	2018
University College Hospital, London	407	11	1979	2018
Unspecified	2		Not recorded	
All	**579**			

Basic demographics

The majority of data published so far on the epidemiology of WM comes from the United States of America, with an reported male-to-female ratio of 2 : 1 and it is higher in Caucasians compared to the Black population (4.1 *versus* 1.8 *per* million *per* year).

In our UK cohort, the male: female ratio is 1.6 : 1 and there are other differences. The lower relative age, median 61 years, of this cohort may reflect specialist centre bias but does serve to highlight the existence of younger patients and raises the question of whether their management should be approached differently.

The ethnic spread is reflective of the cosmopolitan populations in areas such as South East England, which incorporates London, as well as others including Leeds and Birmingham. Patients of Asian origin have greater representation than might have been expected. Possible risk factors for the disease as well as prognostic factors in ethnic subgroups will be a focus of analysis going forwards.

The Rory Morrison Registry: basic demographic data

		Count	Percentage
Gender	Female	219	37.8%
	Male	360	62.2%
Age at diagnosis / years	<40	17	3.0%
	40-49	54	9.6%
	50-59	127	22.7%
	60-69	199	35.5%
	70-79	120	21.4%
	>79	43	7.7%
	Unspecified	19	
Ethnicity	White	386	90.8%
	Black / African / Caribbean / Black British	7	1.6%
	Asian / Asian British	20	4.7%
	Mixed / multiple background	2	0.5%
	Other ethnic group	10	2.4%
	Unspecified	154	

Diagnosis

The table below shows the diagnoses recorded on the Registry and the presenting features in those diagnosed with WM. IgM related conditions, are those where a patient has an IgM paraprotein but do not fulfil criteria to be called WM. This cohort includes conditions such IgM paraprotein related peripheral neuropathy, MGUS and cold agglutinin disease. WM, defined by the presence of >10% LPL in the bone marrow can present asymptomatically or with a range of symptoms.

Clinical manifestations of WM can be divided into lymphoma-related (secondary to tissue infiltration) and paraprotein-related. The IgM paraprotein (or less often IgG or IgA) can lead to symptomatic hyperviscosity, acquired coagulopathies with bleeding and secondary AL amyloidosis in addition to a wide spectrum of autoimmune complications such as cold autoimmune haemolytic anaemia, cryoglobulinaemia, and demyelinating neuropathy.

The table below shows that while the majority of patients on the Registry have a diagnosis of WM, a substantial number have IgM-related conditions. For those with WM, there appears to be an even split between those presenting symptomatically and those without symptoms.

It is important to remember that patients with WM may have clinical problems dominated by the IgM protein even in the context of a low burden of lymphoma cells in the bone marrow. Similarly, those with extensive bone marrow infiltration may have minimal symptoms. The expression of the disease *i.e.,* the type of symptoms must be taken into account alongside volume of disease, whether that be the volume of paraprotein or the percentage infiltrate of LPL in the bone marrow when planning treatment.

Rory Morrison Registry: top-level diagnosis

		Count	Rate
Diagnosis	WM	473	84.0%
	IgM-related	90	16.0%
	Unspecified	16	
WM diagnosis	Asymptomatic	210	48.2%
	Symptomatic	226	51.8%
	Unspecified	37	

Analysis

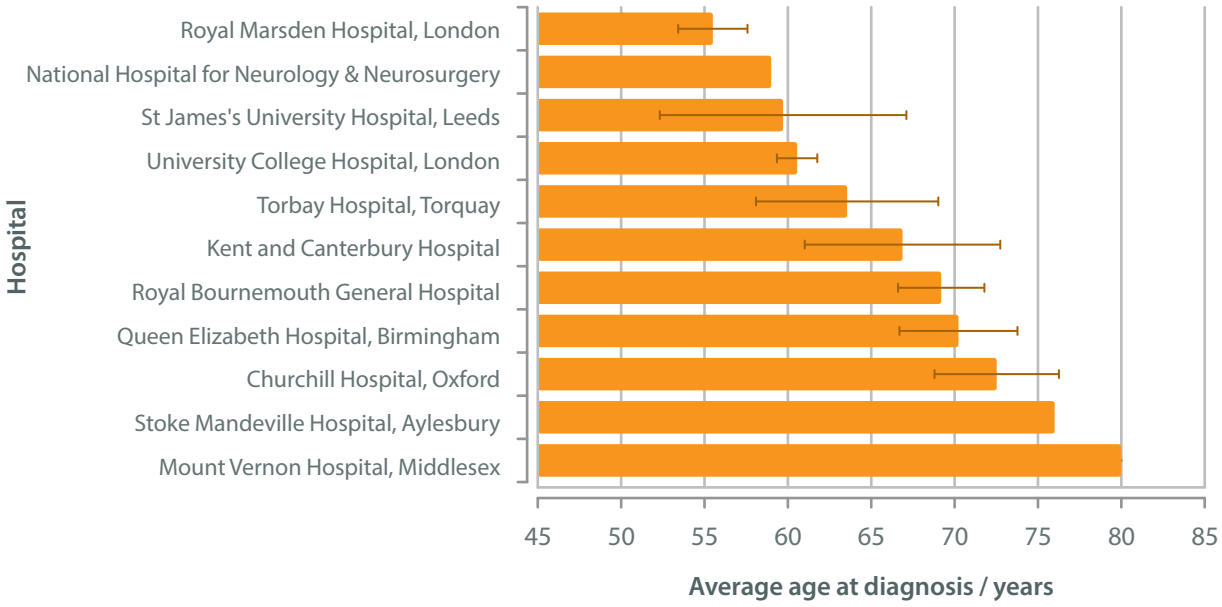
Patients with WM

Age at diagnosis

At the point of diagnosis, there is no way of knowing when the condition actually developed. It is impossible to detect the disease until it declares itself, either as a detectable population of cells in the bone marrow (with the all-important positive 'clonality' [of one kind] tests) or the presence of a monoclonal (M) protein in the blood. Once the condition fulfils criteria for a diagnosis of WM, the journey to treatment is variable in different individuals as they are affected in different ways and have different levels of tolerance for these challenges, depending on their general health and fitness.

The data below shows the average age at diagnosis for patients *per* centre and makes for interesting reading. The Royal Marsden, National Hospital for Neurology, St James's Leeds and University College Hospital are teaching hospitals / specialist centres for lymphoma including WM, so the younger average age is probably a reflection of referral practices to such centres, with patients originating from across the United Kingdom. Royal Bournemouth, a district general hospital is also a specialist referral centre for WM owing to the incumbent clinical expertise but the catchment area has a more senior population.

Patients with WM: Average age at diagnosis (n=469)



Associated conditions

The prevalence of complications and associated conditions with WM is diverse, illustrating the importance for both clinicians and patients to keep WM constantly in the back of their mind.

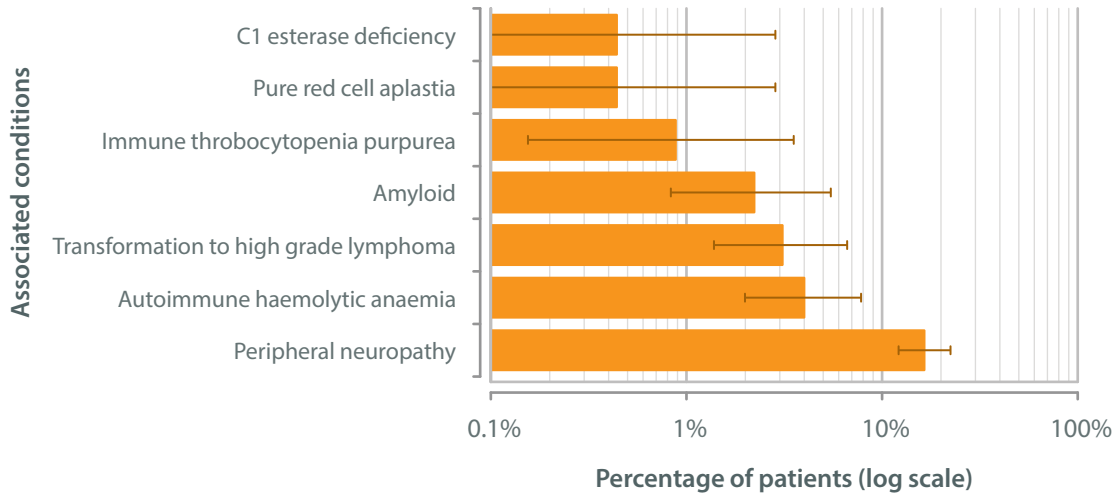
The table below shows the relatively high frequency of peripheral neuropathy in patients with WM. This tends to present with numbness or neuropathic pain and can be caused by the IgM paraprotein targeting the peripheral nerves. The confirmation of cases of peripheral neuropathy and amyloidosis in part reflects the specialism of the joint neuropathy clinics at the largest contributing centre, UCLH. The identification of such complications is crucial to ensure that treatment of appropriate intensity and composition matches the clinical challenges posed by the disease.

Associated conditions such as cold agglutinin disease can now be treated in a more targeted way through novel therapies addressing the so-called complement system. This stops the process of agglutination rather than targeting the underlying B cell population. An awareness of the prevalence of such conditions enables efficient recruitment to clinical trials - another key objective of the Registry.

Patients with a diagnosis of symptomatic WM: associated conditions

Associated conditions	Presence of the condition			
	No	Yes	Unspecified	Rate
Amyloid	217	5	4	2.3%
Peripheral neuropathy	185	37	4	16.7%
Autoimmune haemolytic anaemia	213	9	4	4.1%
Immune throbocytopenia purpurea	222	2	2	0.9%
C1 esterase deficiency	223	1	2	0.4%
Pure red cell aplastia	223	1	2	0.4%
Transformation to high grade lymphoma	216	7	3	3.1%

Patients with symptomatic WM: Associated conditions



IPSSWM

The International Prognostic Scoring System for WM (IPSSWM) comprises 5 criteria: age >65 years; haemoglobin <115 g *per* litre; platelet count <100 x 10^9 *per* litre; β-2 microglobulin >3 mg *per* litre; and monoclonal IgM >70 g *per* litre. Patients who score a 0 or 1 are considered low risk, 2 or whose age is over 65 are intermediate risk, more than 2 is considered high risk.

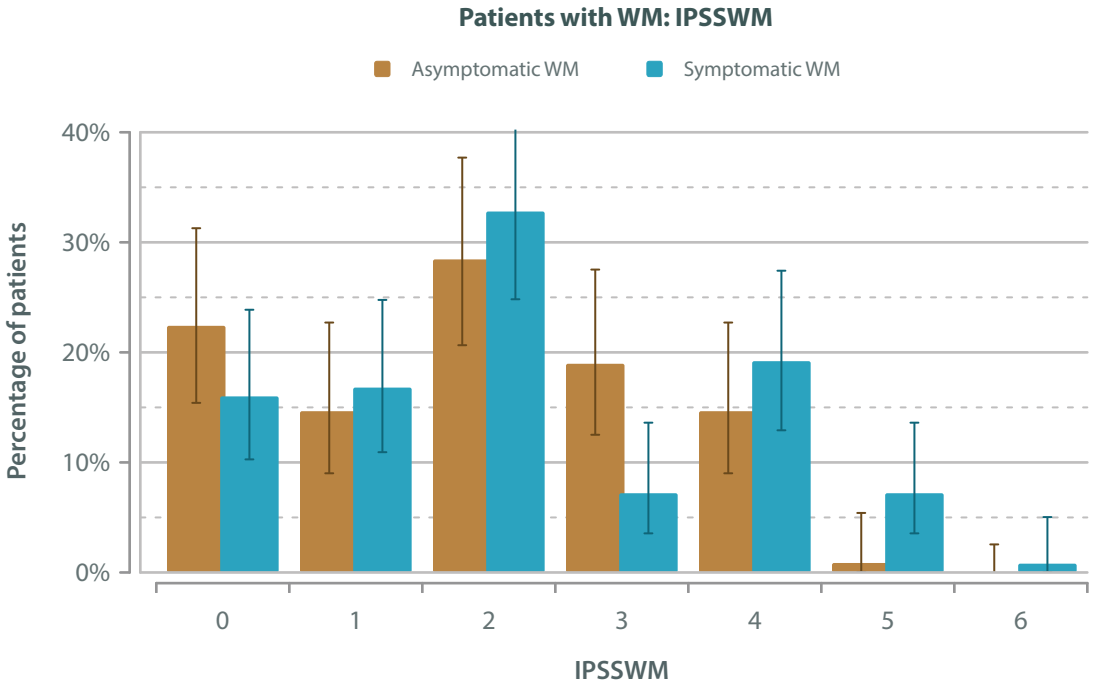
This system is applicable only for patients who need treatment, not as a tool to determine the need for intervention. The criteria are not weighted equally: age has a significant impact; age >65 years contributes to survival outcomes by resulting in classification as intermediate or high risk categorisation, depending on other criteria.

An awareness of the prognostic subgroups in our patient cohort is important to understand the role of different therapies in the risk groups as well as the behaviour of the disease as determined by prognostic parameters.

The substantial number of *unspecified* cases was largely due to missing data, especially the β-2 microglobulin, illustrating the role of registries in highlighting the importance of appropriate testing of patients who are not participating in clinical trials so that the natural history of the disease can be better understood. The IPSSWM is technically validated only at the point of first line treatment, we note the use here is at point of diagnosis, but gives an indication of the spread of prognostic groups at that time.

Patients with a diagnosis of WM: IPSSWM

IPSSWM	WM diagnosis			
	Asymptomatic	Symptomatic	Unspecified	All
0	26	20	2	**48**
1	17	21	1	**39**
2	33	41	4	**78**
3	22	9	3	**34**
4	17	24	1	**42**
5	1	9	1	**11**
6	0	1	0	**1**
Unspecified	94	101	25	**220**
All	**210**	**226**	**37**	**473**



Treatment for WM

Overview

WM, although technically incurable, generally responds very well to treatment and patients can enter a remission that lasts months or years. Trials investigating whether there is any advantage treating patients immediately after they have been diagnosed with WM compared to waiting until they develop symptoms (discussed below) showed no difference in survival advantage and just exposes patients to the side effects of treatment earlier than is necessary. Thus most patients when diagnosed do not require treatment immediately, and are monitored in clinic on a so-called *watch-and-wait* or *active surveillance* approach. This period could be very short or could be for many years, and at present we are unable to predict the length of this period at diagnosis.

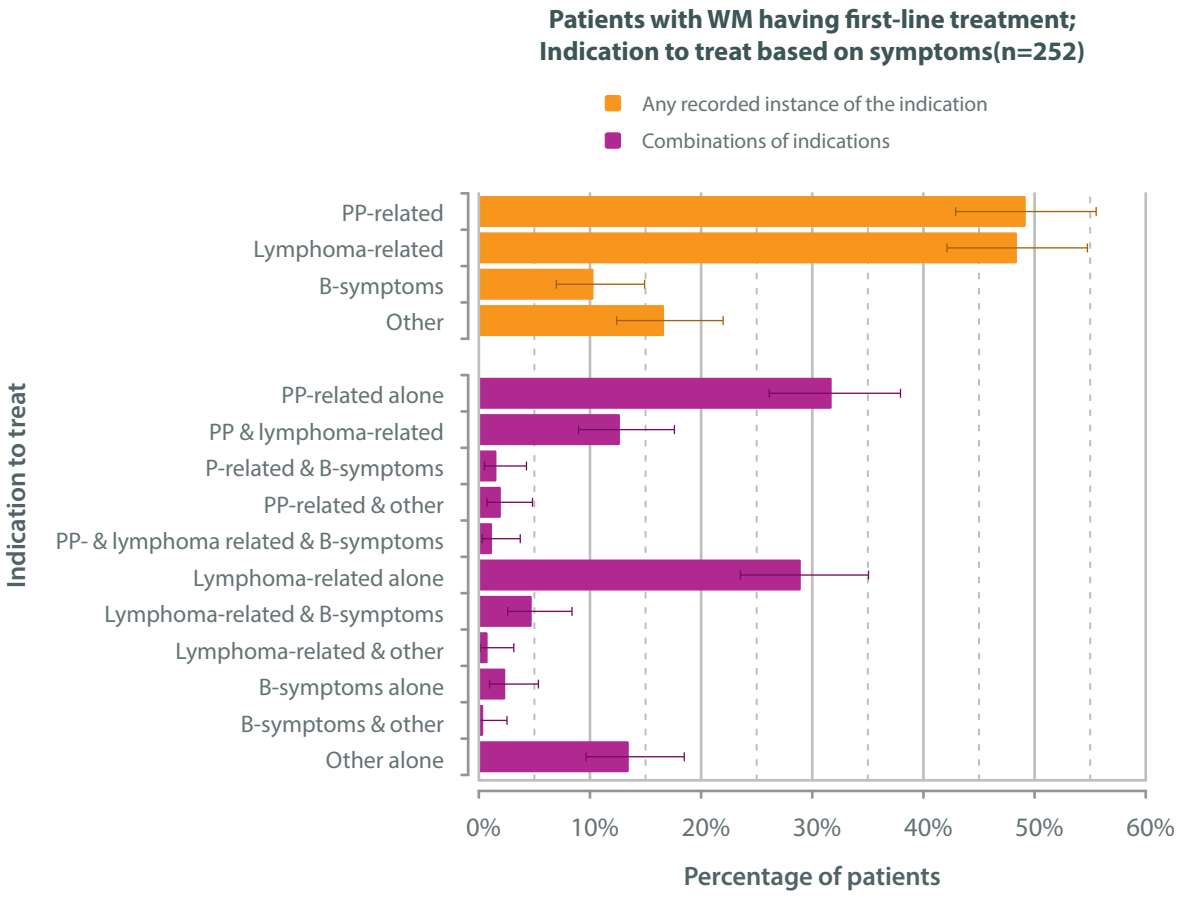
First line treatment

Reasons to start treatment for WM

Patients on active surveillance typically come to clinic every 3-6 months, when they will be asked questions as to whether they are developing symptoms related to the lymphoma and / or paraprotein or rare complications that can occur as a result of WM. They will have a physical examination to look for enlarged lymph nodes, liver or spleen. Bloods will be taken to measure the blood cell counts and IgM paraprotein as well as other routine bloods.

The symptoms related to WM can be very variable but may include B symptoms (loss of weight and night sweats), symptoms related to the lymphoma due to the drop in blood counts, or enlarged lymph nodes or a rising paraprotein. The latter is often the cause of neuropathy (*nerve pains*), hyperviscosity symptoms such as headaches and visual disturbances as well as some rare complications such as amyloid. The decision to treat in some cases can be quite subjective, there are no triggers based on blood counts, paraprotein alone and so the decision is made in partnership with the patient.

The graph below shows the reason why patients had their first treatment commenced. In approximately a third of patients it was due to the paraprotein related symptoms alone and in just over 25% it was due to lymphoma related symptoms alone, with a further 12% due to a combination of the two.

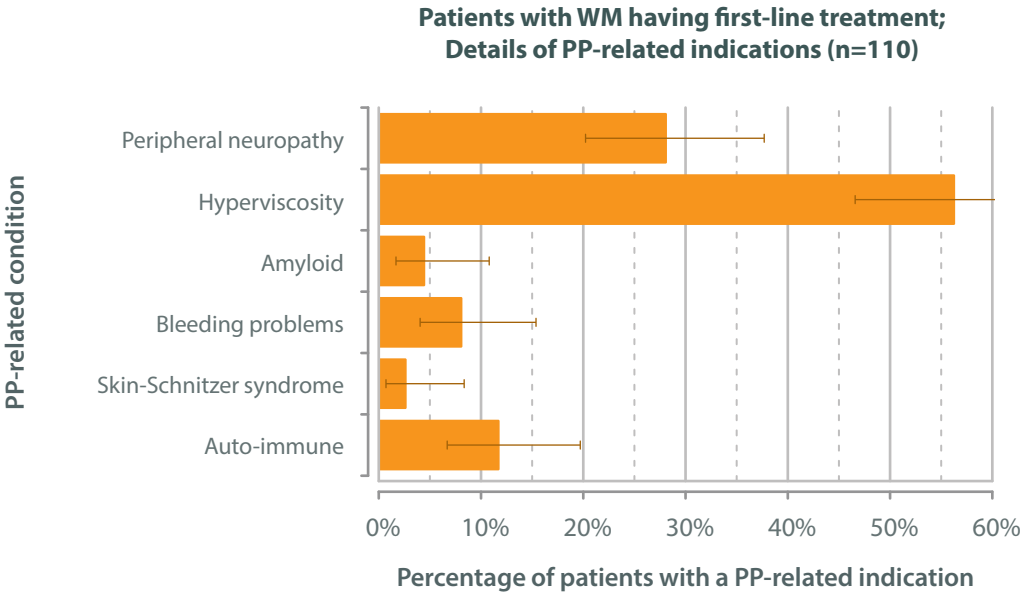


PP-related indications to treat

The table and graph below look at further detail regarding the exact reason for commencing treatment for patients who required it for paraprotein related indications. Over 50% were due to hyperviscosity as a result of a high paraprotein, with just over a quarter related to neuropathy. As expected some of the rarer complications of the paraprotein were the reason for treatment in fewer patients.

Patients with WM undergoing first line treatment: details of PP-related indications to treat

PP-related conditions	Presence of the indication			
	No	Yes	Unspecified	Rate
Peripheral neuropathy	79	31	14	28.2%
Hyperviscosity	48	62	14	56.4%
Amyloid	105	5	14	4.5%
Bleeding problems	101	9	14	8.2%
Skin-Schnitzer syndrome	107	3	14	2.7%
Auto-immune	97	13	14	11.8%



Bone marrow indications

The table below demonstrates the haematological indications for starting treatment *i.e.,* indications based on blood results as opposed to symptoms. Patients with profound anaemia are generally symptomatic expressing significant fatigue, shortness of breath and tiredness. Thrombocytopenia can present with bleeding complications and neutropenia with recurrent infections. We can see here a high proportion of patients with abnormal blood results are anaemic, and the most common haematological indication for starting treatment.

- Anaemia 141 / 142 (unspecified = 174)
- Thrombocytopenia 22 / 142 (unspecified = 174)
- Neutropenia 5 / 142 (unspecified = 174)

A patient's perspective

My WM diagnosis (Sept 2012) was a surprise 65th birthday present. A total protein of 147 and IgM of 81 meant that within days I started plasma exchange and the first of three chemotherapy regimens.

As the three lines of treatment achieved no significant improvement, a stem cell transplant was carried out in March 2014. I had a very good partial response, am not on any medication (WM or other) and have not required further treatment. WM currently has little impact on my life.

Treatment regimens

- 1st line: Rituximab, Cyclophosphamide, Prednisolone (4 cycles) and weekly plasma exchange.
- 2nd line: Rituximab and Bortezomib (4 cycles) and fortnightly plasma exchange.
- 3rd line: Rituximab, Bortezomib, Cyclophosphamide, Dexamethasone (94 cycles) & fortnightly plasma exchange.
- 4th line: Stem Cell *harvest*, ESHAP (x3), Beam autograft.

Approach to treatment

Everyone is different and there is no template for treatment and response.

I consider my responsibility helping achieve a successful outcome relates mainly to fitness, diet, mental attitude and avoidance of infection.

I think of WM as something to be accommodated rather than fought and, fortunately, do not dwell on the if, when and what of WM once again becoming an issue.

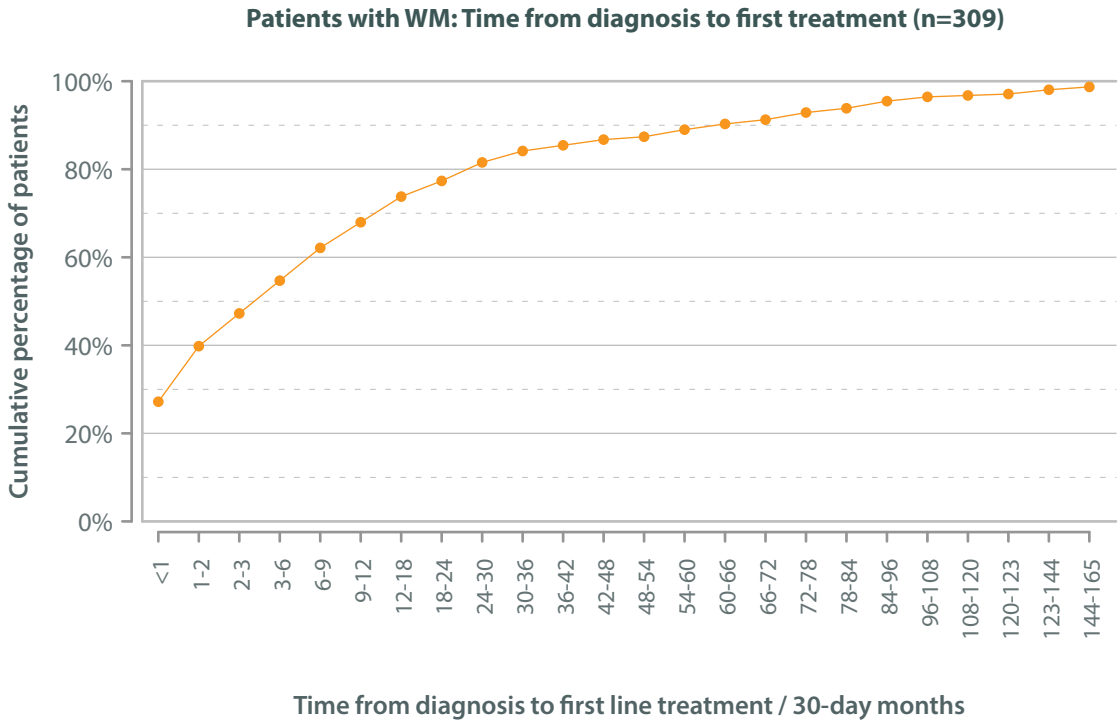
Patient RS

Time to treatment

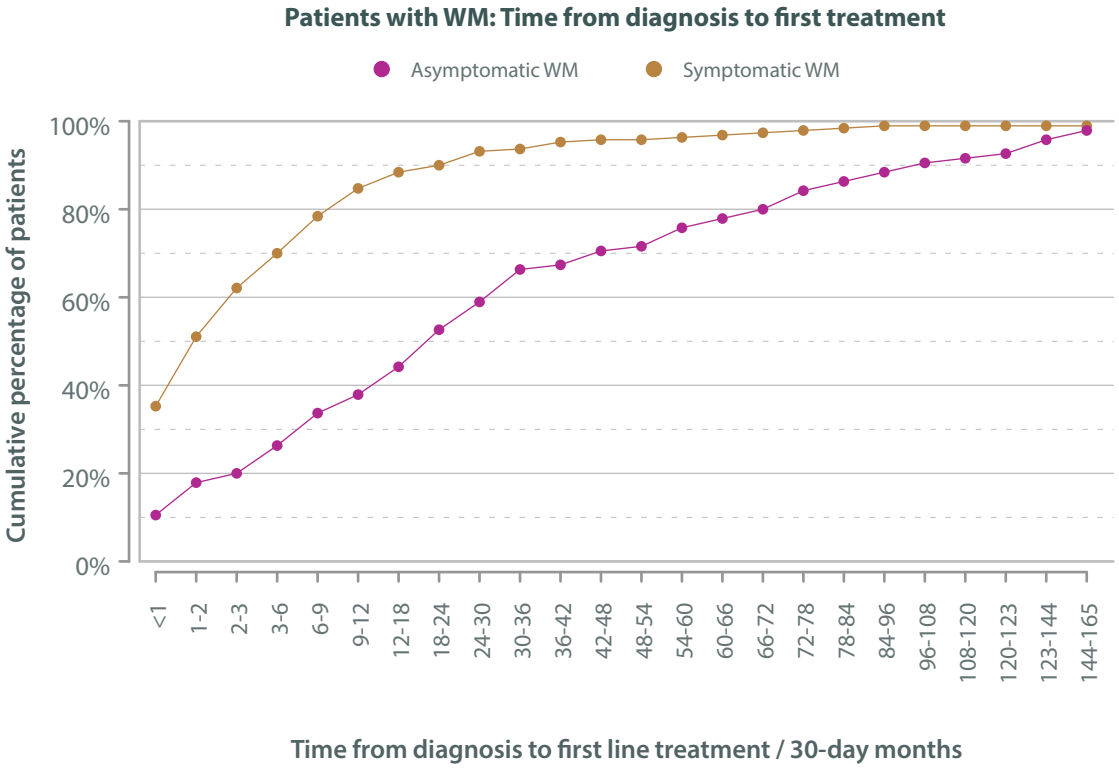
The time between a patient being diagnosed and starting treatment can be very variable for the reasons discussed above. The table and graph below show the time from diagnosis until treatment started for the 309 patients who have been entered onto the Registry and started treatment for WM. Half of patients had started their treatment within 6 months of first being diagnosed. The average length of time from being diagnosed to requiring treatment was just over 1.5 years. However, these figures do not include those patients who are on the Registry who have never required treatment and are still being monitored.

Patients with a diagnosis of WM: time from diagnosis to first line treatment

	Count of patients treated	309
Time from diagnosis to first line treatment / days	Average (95% CI)	589 (462-715)
	Median (IQR)	121 (22-620)
	Minimum	0
	Maximum	9,497



The graph below demonstrates the time from diagnosis to treatment based on whether the patients is symptomatic at diagnosis. As expected there is a shorter time from diagnosis to treatment in patients presenting with symptoms.

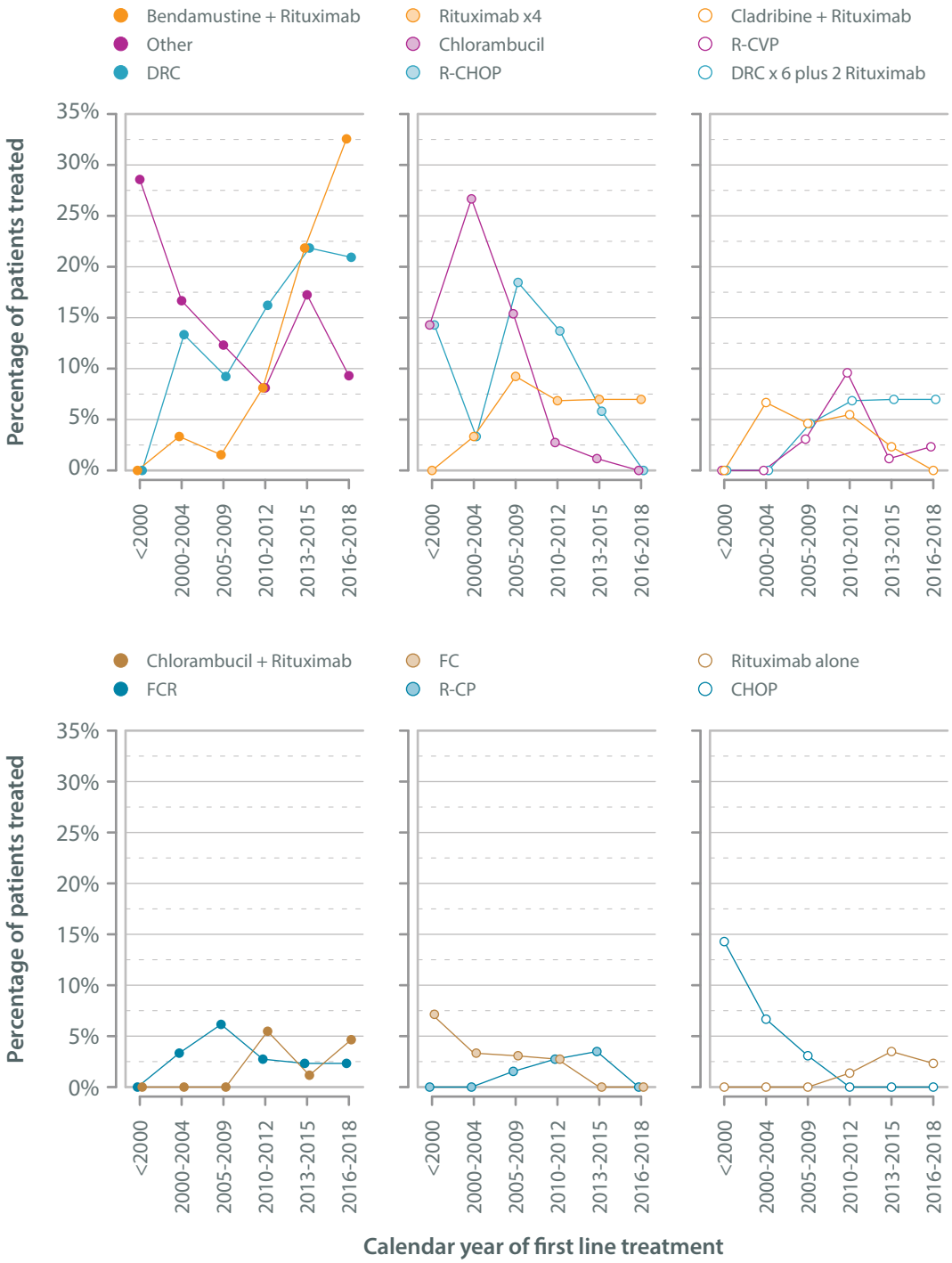


Analysis

Treatments available for patients with WM

There is no defined standard first line treatment for patients with WM, and so the agents patients receive when they require treatment can vary significantly even within the United Kingdom. If there is a clinical trial available, patients should be offered the opportunity to consider entry into the clinical trial, but it should be emphasised that this would be voluntary. At present in the United Kingdom, off trial, most clinicians would prescribe a combination of a monoclonal antibody that targets the CD20 protein that is found on the cell surface of all B lymphocytes including WM cells (usually rituximab) in combination with a chemotherapy agent.

Patients with WM undergoing first line treatment:
Changes in regimen used over time; regimens used most frequently



However, the decision is made on a case-by-case basis, often dependent on the exact indication for treatment and also the expected side effects of the drugs and whether the patient would be able to tolerate them.

The table below highlights the variability in the threatments clinicians prescribe for WM, but the two most common regimens at present for patients who are considered fit enough to tolerate them are rituximab and bendamustine (41 patients in total have received this) and DRC (dexamethasone, rituximab and cyclophosphamide; 51 patients have received this). As well as variation in treatment between different centres, there can be changes in practice over time as new data is published in scientific journals. For example, DRC was not used prior to 2000 even though these drugs were available, but its popularity has increased as its efficacy has been proven.

Patients with WM undergoing first line treatment: treatment regimen

Regimen	Year of diagnosis							
	Not recorded	<2000	2000-2004	2005-2009	2010-2012	2013-2015	2016-2018	All
Allograft stem cell transplant	0	1	1	0	0	0	0	**2**
Bendamustine	0	0	0	0	0	1	1	**2**
Bendamustine + Rituximab	0	0	1	1	6	19	14	**41**
Bortezomib + Dexamethasone + Rituximab	0	0	1	0	2	0	1	**4**
BTK inhibitors	0	0	1	0	0	1	1	**3**
Chlorambucil	0	2	8	10	2	1	0	**23**
Chlorambucil + Rituximab	0	0	0	0	4	1	2	**7**
Chlorambucil and Prednisolone	0	0	0	2	0	0	0	**2**
CHOP	0	2	2	2	0	0	0	**6**
Cladribine + Rituximab	0	0	2	3	4	2	0	**11**
CP	0	0	0	0	1	0	0	**1**
CVP	0	0	1	0	2	1	0	**4**
DRC	1	0	4	6	12	19	9	**51**
DRC x 6 plus 2 Rituximab	0	0	0	3	5	6	3	**17**
FC	0	1	1	2	2	0	0	**6**
FCR	0	0	1	4	2	2	1	**10**
Fludarabine	0	2	0	1	0	0	0	**3**
Fludarabine + Rituximab	0	0	0	1	0	0	0	**1**
MATRIX	0	0	0	0	0	0	2	**2**
Other	0	4	5	8	6	15	4	**42**
R-CHOP	0	2	1	12	10	5	0	**30**
R-CP	0	0	0	1	2	3	0	**6**
R-CVP	0	0	0	2	7	1	1	**11**
Rituximab alone	0	0	0	0	1	3	1	**5**
Rituximab x4	0	0	1	6	5	6	3	**21**
Weekly Cyclophosphamide + Prednisolone	0	0	0	1	0	0	0	**1**
Unspecified	0	0	0	0	1	1	0	**2**
All	**1**	**14**	**30**	**65**	**74**	**87**	**43**	**314**

How to tell whether a treatment has been successful

Patients who are on treatment will be assessed as to whether they are getting any side effects from the treatment (toxicity) and also whether they are responding to the treatment (efficacy). Response will be assessed based on whether any symptoms the patient was experiencing before treatment have improved, physical examination, blood counts, paraprotein level and in some circumstances by repeat scans and bone marrow tests.

For the purposes of comparing how good drugs are to each other, especially in clinical trials, a set of guidelines has been produced by an international group of experts in WM to quantify how good a response a patient achieves, and this is based primarily on the degree of change in IgM paraprotein level compared to the beginning of treatment. Briefly, patients can either respond to treatment, when the paraprotein decreases by 25-50% (minor response), 50-90% (partial response), >90% (very good partial response) or 100% with no other evidence of disease (complete response). If the IgM paraprotein increases by at least 25%, this is considered progressive disease, and if it neither increases by 25% nor decreases by 25% then it is considered stable disease.

The table and graph below show that we know how 249 patients responded to the first treatment they had for WM. Over 80% of patients treated responded to their first treatment, with approximately 10% achieving a minor response, 46% a partial response and over 30% achieving either a very good partial response or complete response.

Patients with WM undergoing first line treatment: treatment response

		Count	Rate
Response	Complete	32	12.9%
	Very good partial	46	18.5%
	Partial	114	45.8%
	Minor	27	10.8%
	Stable disease	25	10.0%
	Progressive disease	5	2.0%
	Unspecified	65	
	All	**314**	

Key things to note when assessing response according to these guidelines is that they are somewhat arbitrary cut-offs for the purposes of categorising patients into groups that one could compare in trials and that from a clinical perspective there is no real difference between someone who achieves a 49% reduction in paraprotein compared to 50%. Furthermore, the response criteria does not take into account whether patients' symptoms improved or not as a result of the treatment and also importantly this measure of assessment does not take into account how long the response lasted and does not necessarily indicate how much time the patient will have before requiring another line of treatment.

Patients with WM undergoing first line treatment: Response to first line treatment (n=249)

Once patients complete their first treatment, the clinician will decide if the patient requires further treatment. If the answer is no (as it will be for most patients), then the patient goes back onto a *watch-and-wait* approach until they develop another reason for requiring further treatment (second line treatment).

The table below shows that of the 473 patients whose data has been entered onto the Registry, 157 have no recorded treatment so far, 149 have only had 1 line of therapy and 4 have had over 8 lines of therapy.

Patients with a diagnosis of WM: lines of treatment

Lines of treatment per patient	WM diagnosis			
	Asymptomatic	Symptomatic	Unspecified	All
None recorded	110	32	15	**157**
1	59	87	3	**149**
2	20	49	6	**75**
3	11	24	2	**37**
4	6	11	4	**21**
5	0	12	0	**12**
6	3	1	4	**8**
7	0	6	1	**7**
8	0	2	1	**3**
>8	1	2	1	**4**
All	**210**	**226**	**37**	**473**

Second line treatment

Regimen

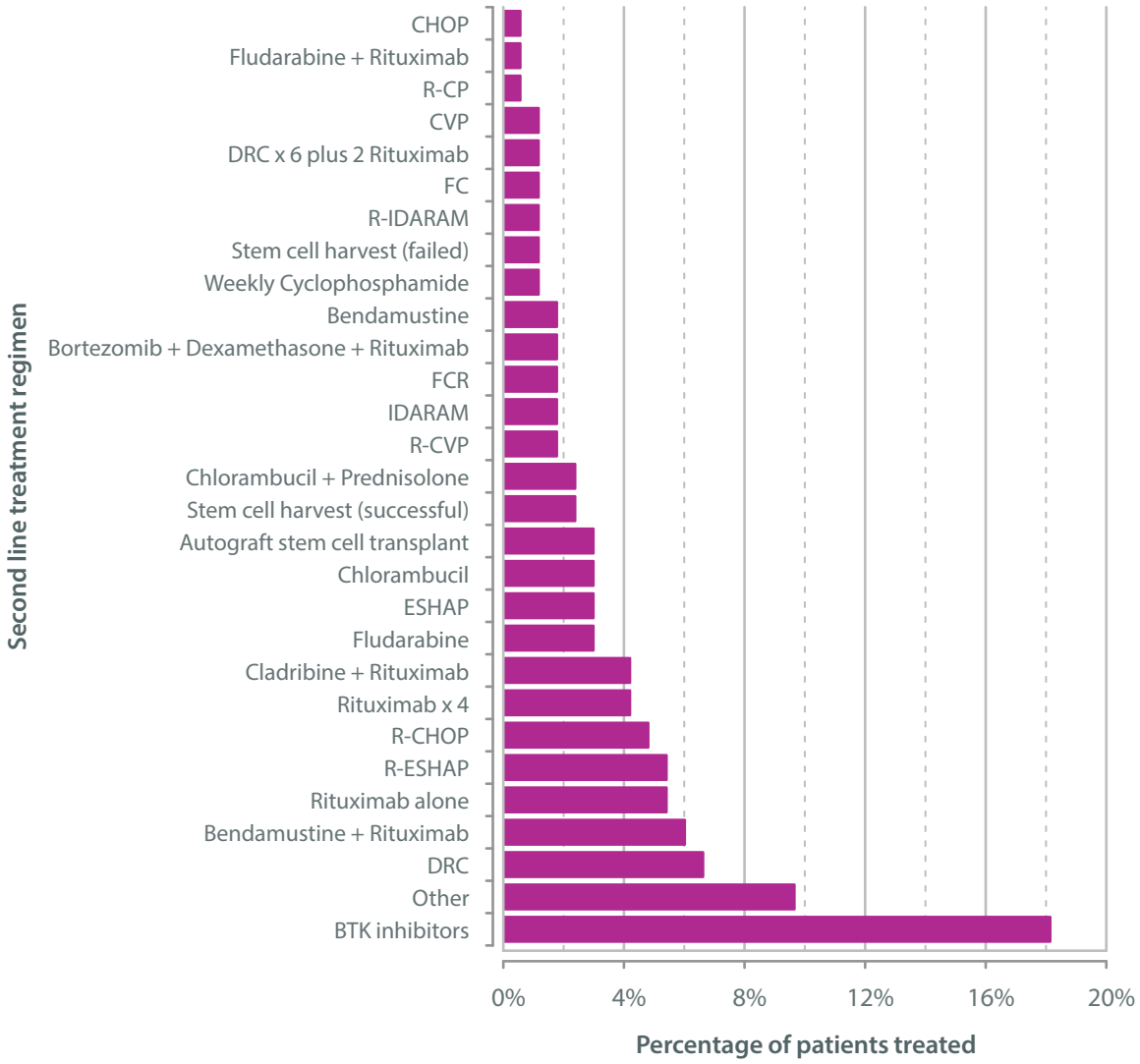
This table and graph show a very large number of different regimens that have been used as second line treatment. The most frequently used treatment was a BTK inhibitor in approximately 18% cases.

This data demonstrates that historically there was no standard treatment for relapsed WM in the United Kingdom. The development of ibrutinib, a first in class BTK inhibitor and then subsequently second generation BTK inhibitors has marked a paradigm shift in treatment of relapsed WM that has rapidly been adopted for relapsed treatment in the United Kingdom. It will be interesting to review future prescribing patterns with increased availability of these drugs *via* the Cancer Drug Fund and further clinical trials.

Patients with WM undergoing second line treatment: treatment regimen

Regimen	Count	Percentage
Autograft stem cell transplant	5	3.0%
Bendamustine	3	1.8%
Bendamustine + Rituximab	10	6.1%
Bortezomib + Dexamethasone + Rituximab	3	1.8%
BTK inhibitors	30	18.2%
Chlorambucil	5	3.0%
Chlorambucil + Prednisolone	4	2.4%
CHOP	1	0.6%
Cladribine + Rituximab	7	4.2%
CVP	2	1.2%
DRC	11	6.7%
DRC x 6 plus 2 Rituximab	2	1.2%
ESHAP	5	3.0%
FC	2	1.2%
FCR	3	1.8%
Fludarabine	5	3.0%
Fludarabine + Rituximab	1	0.6%
IDARAM	3	1.8%
R-CHOP	8	4.8%
R-CP	1	0.6%
R-CVP	3	1.8%
R-ESHAP	9	5.5%
R-IDARAM	2	1.2%
Rituximab alone	9	5.5%
Rituximab x 4	7	4.2%
Stem cell harvest (failed)	2	1.2%
Stem cell harvest (successful)	4	2.4%
Weekly Cyclophosphamide	2	1.2%
Other	16	9.7%
Unspecified	1	
All	**166**	

Patients with a diagnosis of WM undergoing second line treatment: Regimen (n=165)



Time to treatment

The time to next treatment, is the length of time between the end of the last cycle of one treatment regimen and the first cycle of the next regimen. The table and graph below show the time between the first and second lines of treatment. This excludes patients who have not yet relapsed and required a second line of treatment and also excludes patients where the exact dates of treatment finishing is unknown.

The results below suggest a median time to next treatment of 259 days (around 8 months), which would seem significantly shorter than what is currently expected.

This may be due to the all inclusive nature of the table, and further analysis differentiating based on age, symptomatology, treatment and response should be undertaken. However, it does highlight that there maybe a cohort that requires rapid second line treatment.

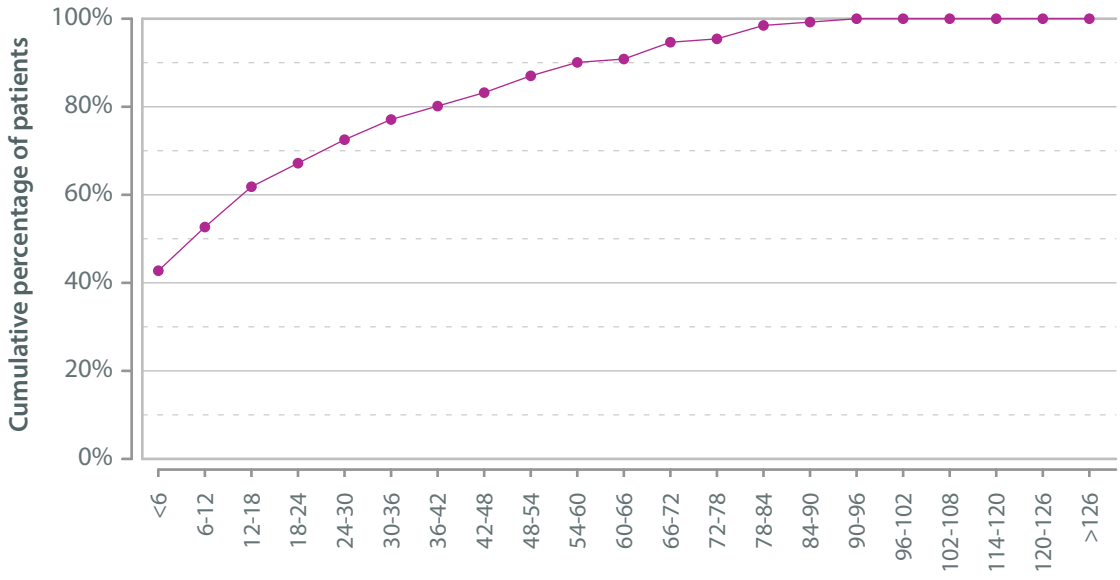
On the other hand, the time between the first and second line treatment can stretch over a decade. Further research needs to be undertaken in this area to develop prognostic and predictive models regarding treatment choices in WM.

Beyond the scope of this report is the assessment from time of biochemical relapse, *i.e.,* a 25% increase in IgM from nadir and the point of symptom development or start of treatment. This will feature in future reports hopefully providing an increased understanding of the natural history of WM.

Patients with a diagnosis of WM: time from first line treatment to second line treatment

	Count of patients	131
Time from first line treatment to second line treatment / days	Average (95% CI)	643 (508-779)
	Median (IQR)	259 (44-944)
	Minimum	0
	Maximum	3,347

Patients with WM: Time from end of first to start of second treatment (n=131)



Response

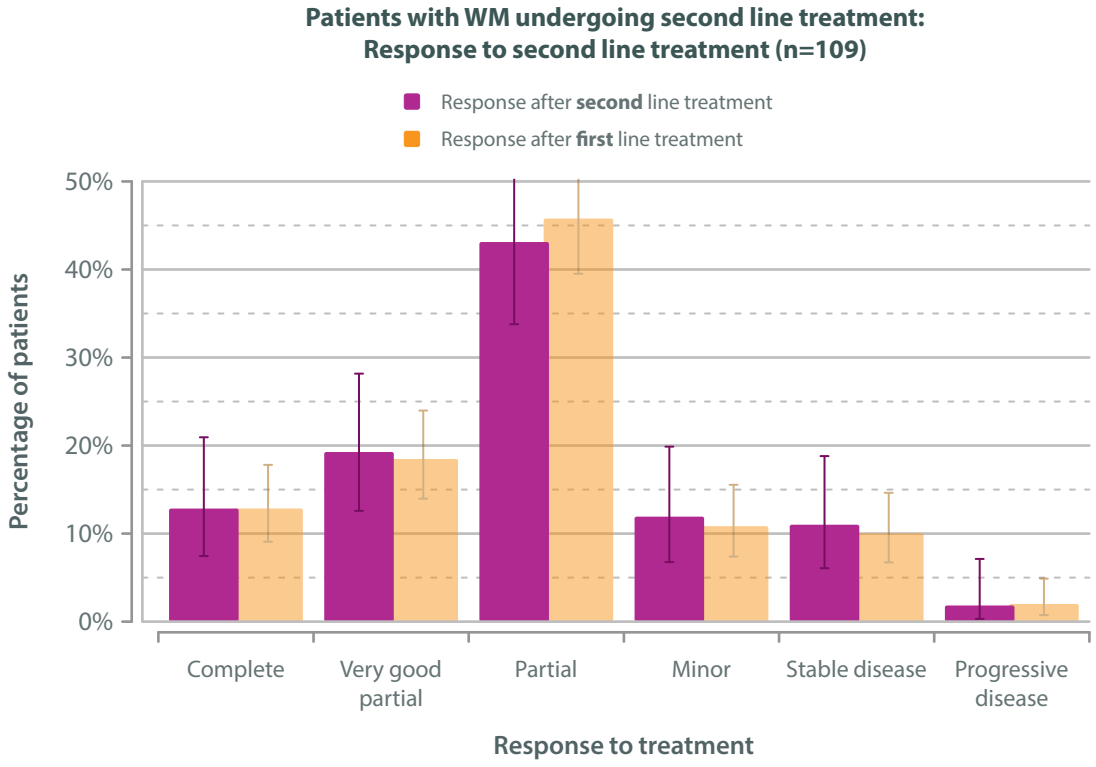
167 patients underwent second line treatment, of which 109 had an investigator-led response criteria reported as *per* International Workshop WM (IWWM) response criteria 2013. The graph demonstrates the difference in response criteria between second line treatment (n=109) and first line treatment (n=249) patients. The overall response rate (ORR) for second line was 87.2% compared to 88.0%

$$\textbf{Overall response rate} = \frac{\text{complete + very good partial + partial + minor}}{\text{known responses}} \times 100\%$$

This data demonstrates very similar response rates at second line *versus* first line. As only 16 % patients received a BTK inhibitor at second line, chemotherapy ± immunotherapy can be an effective treatment in this setting.

Patients with WM undergoing second line treatment: treatment response

		Count	Rate
Response	Complete	14	12.8%
	Very good partial	21	19.3%
	Partial	47	43.1%
	Minor	13	11.9%
	Stable disease	12	11.0%
	Progressive disease	2	1.8%
	Unspecified	58	
	All	**167**	



Specific treatments of interest

Autologous stem cell transplant

Autologous stem cell transplants (ASCT) are funded in the United Kingdom from second line onwards as *per* British Society for Bone Marrow Transplantation (BSBMT) indications. In this cohort, there are 26 patients who underwent ASCT and their data are presented in the table below.

- Second line ×5
- Third line ×8
- Fourth line ×8
- Fifth line ×2
- Sixth line ×1
- Seventh line ×2

BTKi

BTK inhibitors (BTKi) are a class of targeted therapy that have recently been shown to be highly effective in the treatment of WM. Ibrutinib was the first in class with initial phase I data published in 2013, then subsequently the seminal phase II study of 63 relapsed WM patients in 2015 (Treon; New England Journal of Medicine). Further second generation BTKi are currently being evaluated in clinical trials. The trends in BTKi use in the United Kingdom in the last 5 years largely reflects availability of BTKi through clinical trials and then more recently *via* the Cancer Drug Fund after a positive NICE appraisal of ibrutinib use in WM in 2017.

Patients with WM: BTK inhibitors in WM treatment

BTK regimen: Line of treatment	Year of treatment: 2013	2014	2015	2016	2017	2018	All
First	0	0	1	0	2	0	**3**
Second	0	0	7	0	5	18	**30**
Third	0	0	5	0	5	3	**13**
Fourth	0	0	2	0	3	2	**7**
Fifth	0	1	1	0	2	1	**5**
Sixth	0	0	0	0	1	0	**1**
Seventh	1	0	3	0	0	0	**4**
Eight	0	0	0	0	1	0	**1**
Ninth	0	0	1	0	1	0	**2**
Tenth	0	0	0	0	1	0	**1**
All	**1**	**1**	**20**	**0**	**21**	**24**	**67**
Total patients							**66**

Outcomes

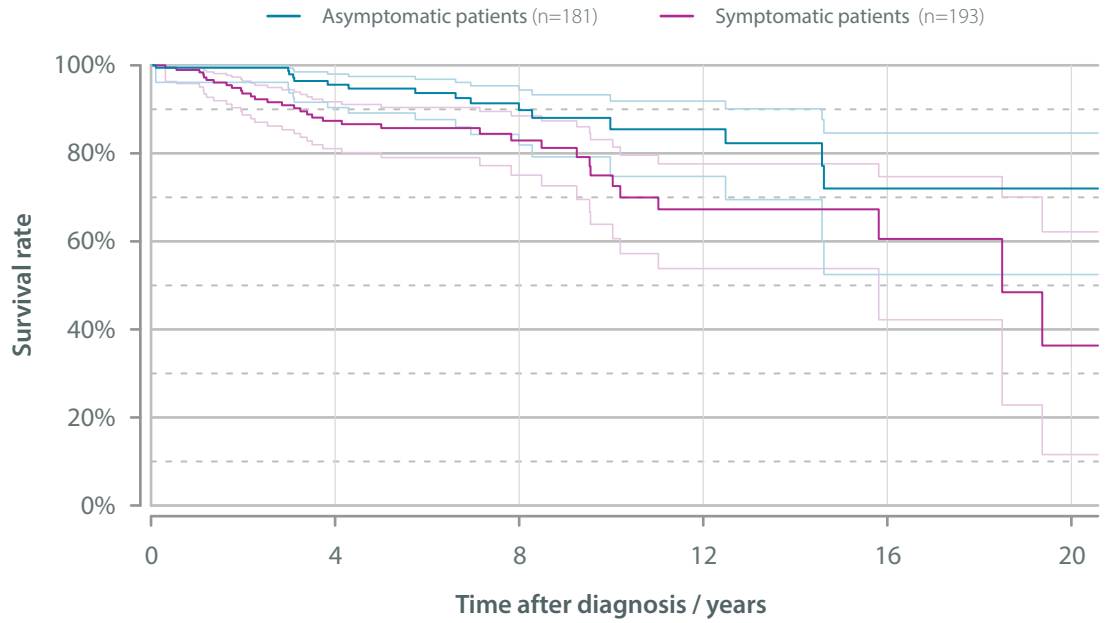
Actuarial survival

Survival and diagnosis

The median overall survival of the symptomatic WM cohort is 18.5 years compared to the median overall survival of the asymptomatic WM cohort which has not yet been reached.

This real-world data, reports a higher overall survival rate than frequently reported in the literature in clinical trials. This probably reflects the referral bias in patients referred to tertiary referral centres for clinical trials.

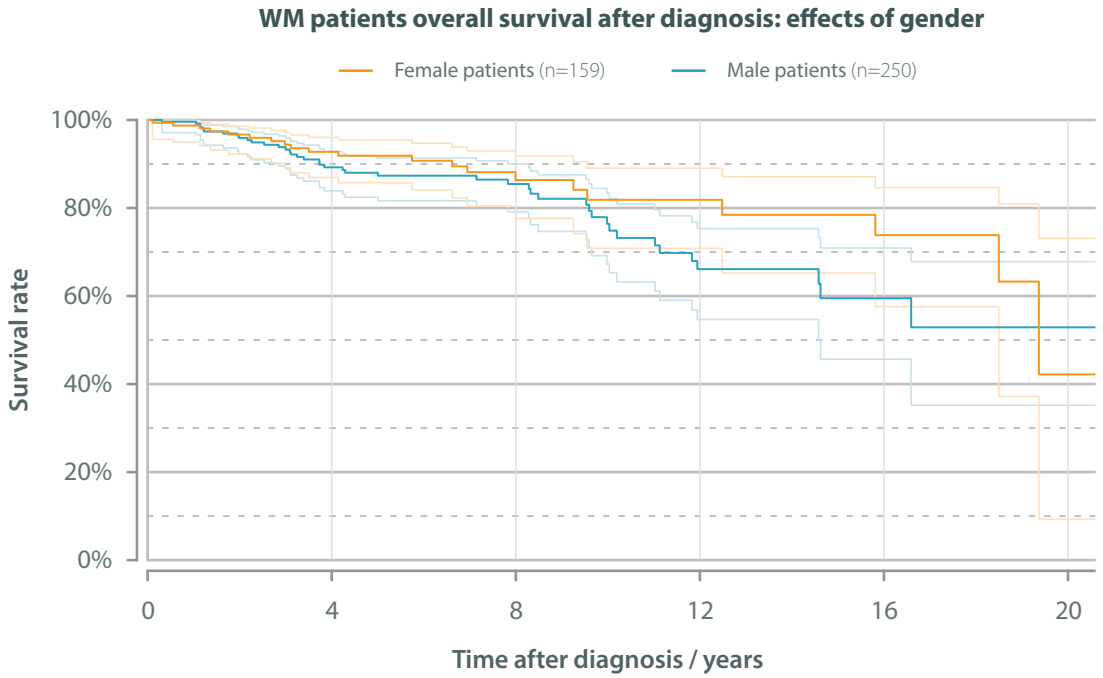
Survival of asymptomatic and symptomatic WM patients after diagnosis



Survival and gender

This graph shows the overall survival of men and women out to 20 years after diagnosis of WM (the recorded data extend beyond 20 years, but are not plotted here because of the low numbers at the extremity). Examining the whole of the data available shows that the median overall survival of men is 29.5 years compared to 19.4 years in women. The cause of the difference in overall survival between men and women is unclear.

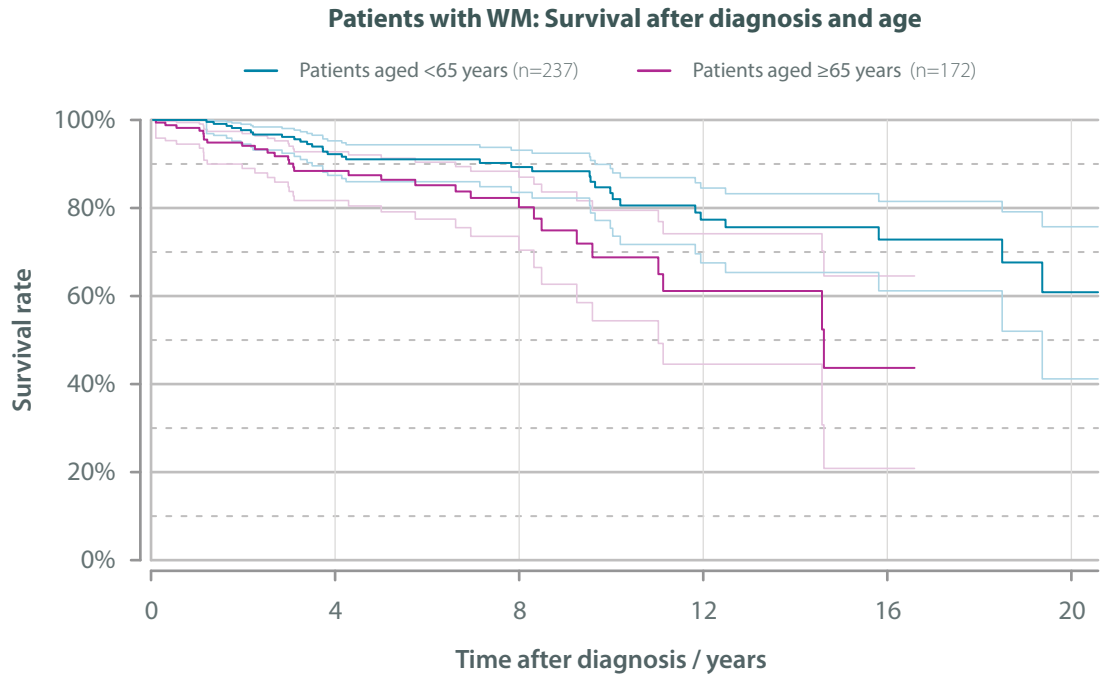
As the Registry accumulates more and more data, these patterns should become clearer.



Survival and age

This graph is a Kaplan-Meier plot showing the difference in overall survival depending on age at diagnosis. The median overall survival for patients diagnosed at >65 years old is 14.6 years compared with 29.5 years for those diagnosed <65 years.

There are a number of factors that are likely to contribute to the worse outcome in the older population such as increasing comorbidities, reduced drug tolerance, and the need for attenuated doses, and death from other causes, but this is an under researched area. There is an unmet clinical need to study the optimum treatment for these older co-morbid WM patients.



High grade transformation

High grade transformation is a recognised and serious complication in patients with WM. The table below demonstrates the number of patients who have evidence of high grade transformation. It is beyond the scope of this report to analyse this cohort, however they warrant further investigation in the future.

- 15 patients in total
- 12 identified at diagnosis
- 10 had one or more treatments where this was an indication
- 2 were flagged up in follow up (and also in a line of treatment record)

A patient's perspective

Like many people with WM I felt something was wrong for some time. More lethargy, breathless climbing hills, bruising more easily. Tests by my GP showed no anaemia. With more obvious symptoms 18 months later and detailed tests low platelets and anaemia were found. A bone marrow biopsy found WM and treatment was needed straight away: diagnosed Christmas Eve 2012! When first told I had NHL there was the inevitable shock. Your head is spinning with so many emotions and thoughts.

Somehow I got a good night's sleep. Woke up and felt like a different person. It was as if my brain had been processing everything while asleep. I knew how I was going to cope and had a plan of action. First get through Christmas and squeeze as much enjoyment from it as possible. Next tell everyone the diagnosis. Next start treatment and educate myself as much as possible about the condition. I now felt a bit more in control and able to cope with whatever lay ahead.

The hardest thing was dealing with everyone else. Knowing it was going to worry my nearest and dearest. Telling my parents who were in their 80s, telling my children. Getting your own thoughts in the right place helps, then you can worry them less. Describing WM as cancer with a little c not a big C was helpful. The stronger and less worried I seemed the less they worried and the better I felt; a positive cycle.

Life was going to split into two parts. Life before cancer and life with cancer; now is the time to find a way to deal with that and help others accept it.

There are certain conversations you never forget. One is being told that you have cancer, another is going for the results of your treatment. For my results I sat opposite my consultant and asked how my bone marrow results were. *alright*, he said … well, alright can mean a lot of things. I asked for clarification. *Your bone marrow looks normal, we could not see any abnormal cells and better still a normal structure has returned.* He had a big smile and so did we.

A very, very happy patient. Life after treatment was unbelievable. I never expected to feel so energetic, in fact I could not remember how many years it had been since I felt this good. Show me a hill and I would want to climb it just because I could.

The next stage of course is watch-and-wait; knowing at some time WM will return. We are all different, but I prefer to understand as much as possible about the condition and possible new treatments. Trying to keep fit and eat healthily must surely help. Is there any truth in turmeric helping?? … well it probably won't hurt so may as well include it in the diet.

Any strange symptom inevitably you wonder is it the WM. At the risk of sounding like a hypochondriac, I jot down anything that is worrying me and mention it at my regular check ups. Writing it down means I don't forget to ask, asking means I am either told it is nothing to worry about or it gets investigated. Either way it is dealt with.

Seeing newer treatments being approved for use in the United Kingdom that are more effective and allow more treatment options make watch-and-wait easier to cope with. There is more hope for our future longevity. The flip side of this is frustration when treatments are available elsewhere but not in the United Kingdom. On balance it is an exciting time to be ill!

Patient LB

Patient Reported Outcomes

Hospital Anxiety and Depression score

Health related Quality of Life (HrQoL) and Patient Reported Outcomes (PRO) are multi-dimensional concepts reflecting the physiological, psychological and social influences of the disease and the therapeutic process from the patient's perspective. Quality of life in WM is of paramount importance due to its chronic relapsing nature, the lack of sufficient information regarding the personal impact of various chemotherapy treatments, and the paradigm shift offered by novel therapies, many of which are administered continuously until progression, rather than for a predefined number of cycles, as is the norm with conventional chemo-immunotherapy.

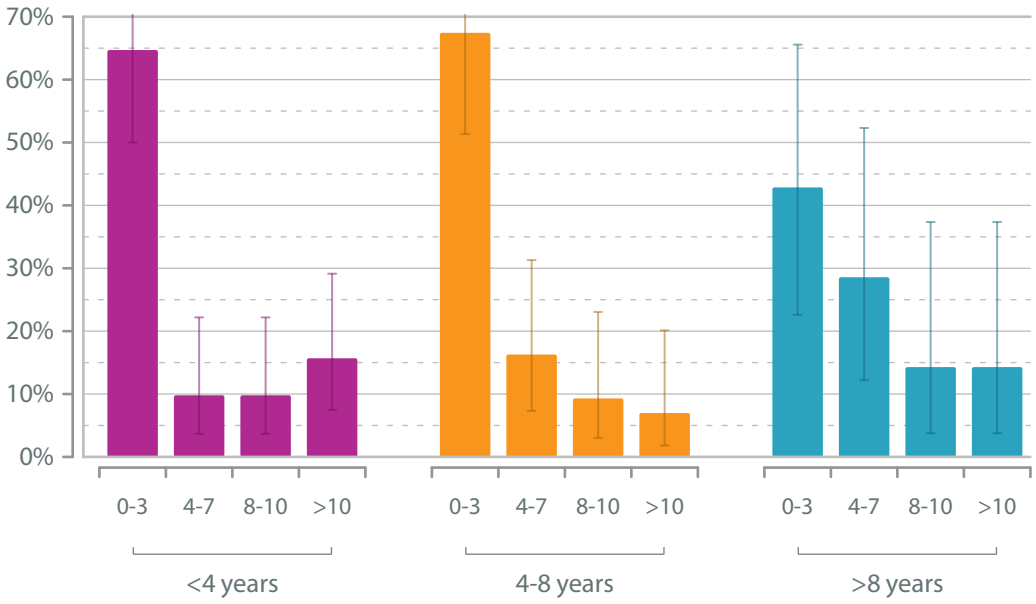
Conventionally, quality of life and PRO has been captured by hand-written questionnaires completed in the outpatient clinic setting. This high-anxiety, time-pressured setting is not ideal for patients to complete PRO questionnaires. Built into the Rory Morrison Registry is the ability to automatically send out PRO questionnaires *via* email for patients to complete in their own home at their leisure.

Since WM is chronic condition with an unpredictable course, the mental health of patients is of critical importance. The Hospital Anxiety and Depression Score (HADS) is a validated method to assess the prevalence of anxiety and depression. Scores between 8 and 10 suggest moderate anxiety and above 10 confirm a diagnosis of anxiety.

The chart below demonstrates results from the HADS questionnaire received from 63 patients through both hand-written forms and online submission. Irrespective of time from diagnosis, anxiety can be present in between 10% and 20% of the population. This significant cohort may benefit from specific referral to cancer support services and psychological support.

Further analysis looking at the impact of treatments, the watch-and-wait programme as well as assessing quality of life using validated tools is the next phase for the PRO extension project.

Patients with WM: HADS anxiety score according to the time elapsed after diagnosis; last recorded score *per* patient



HADS anxiety score and time after diagnosis / years

Future

Future clinical outcomes

The Registry is still in its infancy but has an immense potential to grow in a number of directions. At present, it has limited ability to capture treatment complications but with noticeable variety of different treatments used, this is a key area for development. Identifying the use of supportive care such as blood transfusions, IVIG and plasma exchange will also be an essential area for understanding. Such interventions are rarely picked up by NHS data capture systems in a joined-up way. As a result important morbidities experienced by the patient, and extra expenditure for the NHS will be missed.

One of the least understood areas in WM is the point at which patients need to be treated, especially upon relapse. Biochemical relapse, defined as an increase of >25% in IgM paraprotein, can occur will before a patient becomes symptomatic. Conventionally, treatment is determined by symptoms, rather than biochemical relapse, but identifying patients early who are at risk of rapid symptomatic progression and early requirement of treatment, would prove invaluable.

Further UK recruitment

At present only 7 centres have entered a significant amount of data and another 8 centres are awaiting confirmation from local trials units prior to data entry. The main hurdles for data upload are local approval and funding for data managers. There is a significant variability between centres with respect to the degree of local approval. In order to attain local resources such as a data acquisition team, then approval from the local trials team is generally required. This is a time consuming process and delays data entry, however is necessary to ensure high quality data entry.

Patients, through WMUK, have been very vocal in support of the Registry and have encouraged consultants to upload data or to register the hospital with the Rory Morrison Registry. At present over 40 centres have demonstrated interest in the Registry, and with the production of the annual report as a clear example of what is achievable, alongside a streamlining of the recruitment process, we would hope to over centres registered within the next 12 months. This would translate to having over one thousand patients registered, making it the largest WM registry worldwide.

Outpatient tool

The main objective of the Registry is to capture the landscape of WM in the United Kingdom. The Registry can also be used in the outpatient clinic setting to directly inform the clinician of a patients' trend in parameters such as haemoglobin, IgM or paraprotein. It also provides a clear timeline of diagnostic information and treatment responses. With updates to the user interface the Registry will become an integral part of outpatient clinic appointments.

New treatments

With a raft of new treatments being developed for WM, the Registry will play a critical role in surveillance and assessment of new treatments in the real world setting. Recognised by NICE and the CDF, the Registry will be used in the appraisal of ibrutinib in November 2019 and likewise with newer treatments.

Further ahead the Registry will be used as a hypothesis generating tool and precursor to research by identifying abnormal patterns in response or cohorts of patients. With the ongoing use and development of genetic testing, such as MYD88 and CXCR4, the Registry will be able to provide a comprehensive overview of the natural history in patients with varying genetic abnormalities in the real world context.

Conclusion

The Rory Morrison Registry is a true collaborative effort between patients and clinicians. The report highlights some of the critical findings from the Registry, but has barely scratched the surface of the Registry's potential. With continued expansion, regular data entry and constant patient involvement and drive, the Registry will be an immense force that will drive the use of novel therapies in the United Kingdom, improve and standardise care, and contribute to the global research effort in understanding a complex condition.

Contributors to the report

Dr Joshua Bomsztyk

WM Clinical Fellow and RMR Fellow

Author of the Executive Summary, background, registry schematic, regulation and mechanics, registry demographics, PRO and future sections.

Having worked on the Registry for over year, I see the immense potential the Registry has for the betterment of care for patients with WM in the United Kingdom; it has been an absolute privilege to work on this project.

Dr Shirley D'Sa

Consultant Haematologist, UCLH and RMR Project Lead

Author of the Introduction and section on patient demographics.

Supporters of WMUK have generously donated funds to develop this Registry; we are immensely grateful for this and are pleased to present these initial analyses, which we are certain will help to inform more effective clinical practice going forwards.

Dr Helen McCarthy

Consultant Haematologist, Royal Bournemouth Hospital, Member of the Medical Advisory Board WMUK and WMUK Trustee

Author of section of treatment in the relapsed setting.

I am delighted to see our vision of a National WM database come to fruition and it is already providing insightful & valuable real world data.

Dr Dima El-Sharkawi

Consultant Haematologist, Royal Marsden

Author of section on first line treatment.

The Registry is an amazing resource that will help us better understand WM by pooling our collective experience in individual centres together.

Dr Guy Pratt

Consultant Haematologist, Queen Elizabeth Hospital, Birmingham and WMUK Trustee

Author of section on patient outcomes and survival.

I have been a Trustee for WMUK since 2013 and feel passionately about improving support and treatment for patients with WM.

Dr Harriet Scorer

Patient representative WMUK and WMUK Trustee

This Registry is an important step towards understanding WM and its treatments in the United Kingdom.

Roger Brown

Chairman of WMUK

The success of the Registry is the best news ever for UK Waldenstrom patients in the long term.

Appendix

A note on the conventions used throughout this report

There are several conventions used in the report in an attempt to ensure that the data are presented in a simple and consistent way. These conventions relate largely to the tables and the graphs, and some of these conventions are outlined below.

The specifics of the data used in any particular analysis are made clear in the accompanying text, table or chart. For example, many analyses sub-divide the data on the basis of diagnosis, and the titles for both tables and charts will reflect this fact.

Conventions used in tables

On the whole, unless otherwise stated, the tables and charts in this report record the number of procedures (see the example below).

Patients with a diagnosis of WM: IPSSWM

		WM diagnosis			
		Asymptomatic	Symptomatic	Unspecified	All
IPSSWM	0	26	20	2	**48**
	1	17	21	1	**39**
	2	33	41	4	**78**
	3	22	9	3	**34**
	4	17	24	1	**42**
	5	1	9	1	**11**
	6	0	1	0	**1**
	Unspecified	94	101	25	**220**
	All	**210**	**226**	**37**	**473**

Each table has a short title that is intended to provide information on the subset from which the data have been drawn, such as the patient's gender or particular operation sub-grouping under examination.

The numbers in each table are colour-coded so that entries with complete data for all of the components under consideration (in this example both IPSSWM score and WM diagnosis) are shown in regular black text. If one or more of the database questions under analysis is blank, the data are reported as unspecified in orange text. The totals for both rows and columns are highlighted as emboldened text.

Some tables record percentage values; in such cases this is made clear by the use of an appropriate title within the table and a % symbol after the numeric value.

Rows and columns within tables have been ordered so that they are either in ascending order (age at procedure: <20, 20-24, 25-29,30-34, 35-39 years, *etc.*; post-procedure stay 0, 1, 2, 3, >3 days; *etc.*) or with negative response options first (No; None) followed by positive response options (Yes; One, Two, *etc.*).

Row and column titles are as detailed as possible within the confines of the space available on the page. Where a title in either a row or a column is not as detailed as the authors would have liked, then footnotes have been added to provide clarification.

There are some charts in the report that are not accompanied by data in a tabular format. In such cases the tables are omitted for one of a number of reasons:

- insufficient space on the page to accommodate both the table and graph.
- there would be more rows and / or columns of data than could reasonably be accommodated on the page (for example, Kaplan-Meier curves).
- the tabular data had already been presented elsewhere in the report.

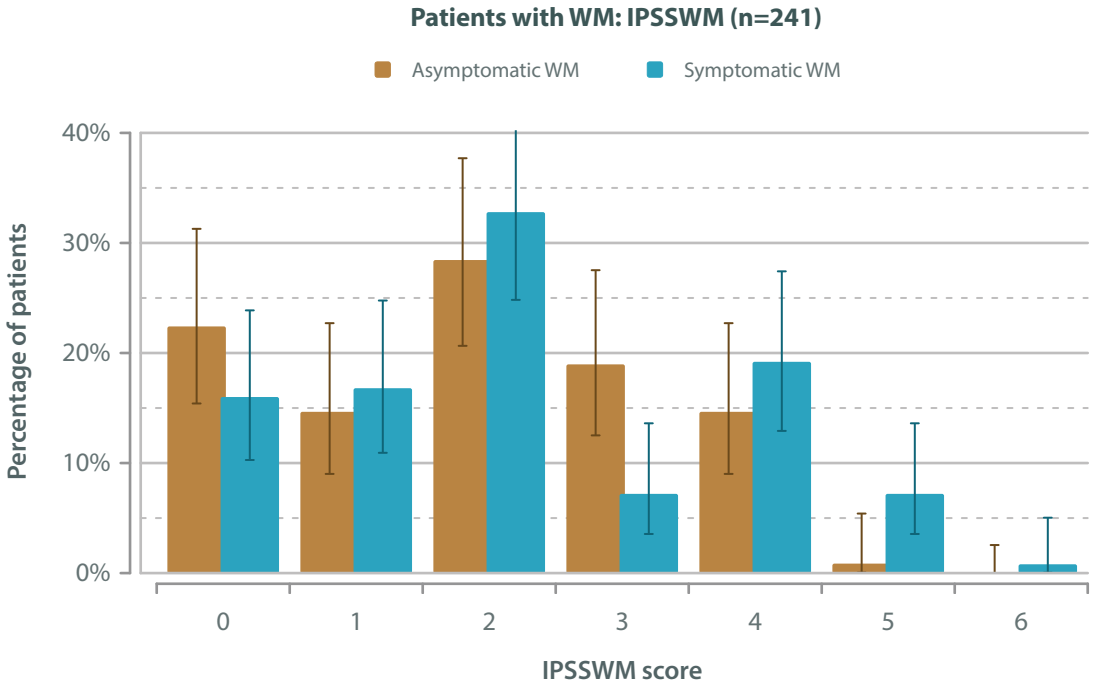
Conventions used in graphs

The basic principles applied when preparing graphs for this First UK WM Registry Report were based, as far as possible, upon William S Cleveland's book *The elements of graphing data* [1]. This book details both best practice and the theoretical bases that underlie these practices, demonstrating that there are sound, scientific reasons for plotting charts in particular ways.

Counts: The counts (shown in parentheses at the end of each graph's title as n=) associated with each graph can be affected by a number of independent factors and will therefore vary from chapter to chapter and from page to page. Most obviously, many of the charts in this report are graphic representations of results for a particular group (or subset) extracted from the database, such as patients with a diagnosis of WM. This clearly restricts the total number of database-entries available for any such analysis.

In addition to this, some entries within the group under consideration have data missing in one or more of the database questions under examination (reported as unspecified in the tables); all entries with missing data are excluded from the analysis used to generate the graph because they do not add any useful information.

For example, in the graph below, only the records where the patient has a WM diagnosis **and** both the patient's symptomatic status and IPSSWM score are known are included; this comes to 241 patient-entries (26 + 17 + 33 + 22 + 17 + 1 + 0 + 20 + 21 + 41 + 9 + 24 + 9 + 1; the 232 entries with unspecified data are excluded from the chart).



Confidence interval: In the charts prepared for this report, most of the bars plotted around rates (percentage values) represent 95% confidence intervals [2]. The width of the confidence interval provides some idea of how certain we can be about the calculated rate of an event or occurrence. If the intervals around two rates do not overlap, then we can say, with the specified level of confidence, that these rates are different; however, if the bars do overlap, we cannot make such an assertion.

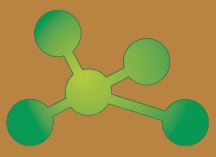
Bars around averaged values (such as patients' age, post-operative length-of-stay, *etc.*) are classical standard error bars or 95% confidence intervals; they give some idea of the spread of the data around the calculated average. In some analyses that employ these error bars there may be insufficient data to legitimately calculate the standard error around the average for each sub-group under analysis; rather than entirely exclude these low-volume sub-groups from the chart their arithmetic average would be plotted without error bars. Such averages without error bars are valid in the sense that they truly represent the data submitted; however, they should not to be taken as definitive and therefore it is recommended that such values are viewed with extra caution.

1. Cleveland WS. *The elements of graphing data*. 1985, 1994. Hobart Press, Summit, New Jersey, USA.
2. Wilson EB. Probable inference, the law of succession, and statistical inference. *Journal of American Statistical Association*. 1927; **22**: 209-212.

First UK Waldenström's Macroglobulinaemia Registry Report

The registry is constantly looking to expand the number of patients and centres involved; if you are interested then please contact WMUK using the e-mail address: **registry@wmuk.org.uk**

For more information about WM, the condition, its treatments and the United Kingdom support network visit the WMUK website: **www.wmuk.org.uk**



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