Institution: Queen's University Belfast

Unit of Assessment: UoA3

Title of case study: Improving treatment and quality of life for patients with Myeloproliferative Neoplasms

Period when the underpinning research was undertaken: 2000-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Mary Frances McMullin	**Professor of Clinical Haematology**	**1/11/1991 to present**

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Myeloproliferative neoplasms (MPNs) affect *ca.* 9,000 people in the UK annually. There is an extensive unmet need as current treatments are inadequate to control and eliminate disease. Professor McMullin has led and contributed to pivotal international trials in MPN diseases with the following significant impacts:

- Primary Thrombocythaemia-1 (PT-1) is the **largest randomised trial for** essential or primary thrombocythaemia (ET or PT) **in the world. Changes to treatment** of ET **have saved the NHS *ca.* GBP7,000,000 per year** while other drugs shown to be ineffective, have not been further developed.
- (Inter)national guidelines for patient management have been developed from trial results, **improving treatment** and **quality of life** for patients across the globe.

2. Underpinning research

The haematology group in Queen's has existed since 1980, with an original focus on control of erythropoiesis. Prof. McMullin developed this area and expanded into the related MPNs both from a clinical and laboratory aspect. She works with other members of the group, *i.e.* Prof Ken Mills on epigenetics using trial samples.

MPNs: The types of MPNs are polycythaemia vera (PV), essential thrombocythaemia (ET) (previously known as primary thrombocythaemia, PT) and myelofibrosis (MF). The disorders are associated with thromboembolic and haemorrhagic events leading to complications, progression to myelofibrosis and acute leukaemia with shortened life expectancy. The annual worldwide incidence rates for PV, ET and MF are 0.84, 1.03 and 0.47 per 100,000 population. Although these are rare disorders, the prevalence rates are many times higher as the patients survive for years with an ongoing burden of complications and symptoms.

Clinical trials which demonstrated treatment advances for MPNs

The national Primary Thrombocythemia-1 (PT-1) trial investigated treatments in all risk groups of PT. Prof. McMullin and the group have been **leaders** within this trial since 1996. In total, 806 patients participated in the trial making this **the largest randomised trial in this disorder in the world**. The intermediate arm of the trial has recently completed and reported that **intermediate risk patients could avoid hydroxycarbamide for cytoreduction** with significant implications for individual patients and the overall NHS **[3.1].**

The group also contributed to many other trials in the field including groundbreaking commercial trials such as COMFORT-II, one of the licensing trials for ruxolitinib, the JAK inhibitor, **which is now the first line treatment for MF [3.2]**.

The MAJIC trial is an-investigator led randomised phase II 5 year-trial of best available therapy versus JAK inhibition in patients with PV or ET-resistant or intolerant of hydroxycarbamide started in 2012. Prof. McMullin has been one of the **national leaders**, initiating and developing this trial, which shows that **ruxolitinib is effective as second line treatment (**after the initial treatment (first-line treatment) has failed) **in PV [3.3]**.

Clinical trials contributing to decision making in drug development
The Histone deacetylase (HDAC inhibitor) vorinostat showed activity in other haematological malignancies and is licensed for the treatment of T-cell lymphoma. Prof. McMullin and Prof. H. Hasselbalch from Denmark (**both lead investigators**) developed an investigator-led trial (MK-0683) of this compound in MPNs carried out in multiple sites in the UK and Denmark started in 2009. This trial showed that **the drug was effective** in controlling blood counts in these disorders but **with a lot of toxicity [3.4, 3.5]**. It was therefore not commercialized for MPNs by the pharmacological company, however, **it is still used to treat some patients with MPNs for whom no other therapy is effective** on a named patient basis.

Another HDAC inhibitor, **givinostat, has shown to be effective** in a phase II trial (NCT01761968) in MPNs where Prof. McMullin was a **UK lead** across multiple sites **[3.6].** This agent **is now being taken forward in a licensing phase III trial** [DSC/08/2357/32] in PV.

3. References to the research

3.1. Godfrey AL, Campbell PJ, MacLean C, Buck G, Cook J, Temple J, Wilkins BS, Wheatley K, Nangalia J, Grinfeld J, **McMullin MF**, Forsyth C, Kiladjian JJ, Green AR, Harrison CN. Hydroxycarbamide plus aspirin versus aspirin alone in patients with essential thrombocythaemia age 40 to 59 years without high-risk features. Journal of Clinical Oncology 2018 Aug 28 PMID: 30153096, cited by 8 (May 2020).

3.2. McMullin MF, Harrison CN, Niederweiser D, Demuynuk H, Jakel N, Gopalakrishna P, McQuitty M, Stalbovskaya V, Recher C, Theuissen K, Gisslinger H, Kiladjian JJ, Al-Ali HK. The use of erythropoiesis stimulating agents with ruxolitinib in patients with myelofibrosis in COMFORT-II: an open-label, phase3 study assessing efficacy and safety of ruxolitinib versus best available therapy in the treatment of myelofibrosis. Experimental Hematology Oncology (2015) 15; 4: 26: PMID: 26380150, cited by 27 (May 2020).

3.3. Harrison CN, Mead AJ, Panchal A, Fox S, Yap C, Gbandi E, Houlton A, Alomam S, Ewing J, Wood M, Chen F, Coppell J, Panoskaltsis N, Knapper S, Ali S, Hamblin A, Scherber R, Dueck AC, Cross NCP, Mesa R, **McMullin MF**. Ruxolitinib versus best available therapy for ET intolerant or resistant to hydroxycarbamide in a randomised trial. Blood 2017 130(17):1889-1897 PMID: 29074595, cited by 60 (May 2020).

3.4. Andersen CL**, McMullin MF**, Ejerblad E, Zweegman S, Harrison C, Fernandes S, Bareford D, Knapper S, Samuelsson J, Lofvenberg E, Linder O, Andreasson B, Ahlstrand E, Jensen MK, Bjerrum OJ, Vestergaard H, Larsen H, Klausen TW, Mouritis-Andersen T, Hasselbalch, HC. A phase II study of vorinostat (MK-0683) in patients with polycythaemia vera and essential thrombocythaemia. British Journal of Haematology (2013) Aug; 162(4) 498-508. PMID: 23758082, cited by 59 (May 2020).

3.5. McPherson S, Greenfield G, Anderson C, Grinfield J, Hasselbalch H, Nangalia J, Mills KI, **McMullin MF**. Methylation age as a correlate for allele burden, disease status and clinical response in myeloproliferative neoplasm patients treated with Vorinostat. Experimental Hematology. (2019) 79: 26-34. PMID: 31563618.

3.6. Rambaldi A, Iurio A, Vannucchi A, Noble R, von Bubnoff N, Guarini A, Martino B, Pezzutto A, Carli G, De Muro M, Luciani S, **McMullin MF**, Cambier N, Marolleau J-P, Mesa RA, Tibes R, Pancrazzi A, Gesullo F, Bettica P, Manzoni S, Di Tollo S. Safety and efficacy of the maximum

tolerated dose of givinostat in polycythemia vera: A two-part phase Ib/II study Leukemia (2020) PMID: 32047238, cited by 1 (May 2020)

4. Details of the impact

Marked Improvement in Treatment Options for People with MPNs.

The QUB Haematology group has had a major **impact on patient management** at different levels. At local Northern Ireland (NI) level, in the last **10 years approximately 120 patients** (Figures from Northern Ireland Cancer Trials Network) have entered into MPN trials giving them the opportunity to receive **new and state-of-the-art treatment** and the **most advanced investigation** of their disease **[5.1].** These are rare disorders and it is usually only patients, who are intolerant or refractory to first line treatments, are eligible for trials, **therefore providing these patients with a treatment option that is not routinely available as part of standard care.**

With a stable population of approximately 200 MPN patients in the greater Belfast area and referrals from all of NI, the number entering trials represents a substantive proportion of the MPN population in NI. All patients with MPNs in NI are referred to the myeloid multi-disciplinary meeting (MDM) in Belfast Health and Social Care Trust or via their local MDM to this meeting for opinion on their disease and thus are referred for trials as appropriate.

At national and international level, this work has led to **new and improved treatments** for patients with MPNs. The MAJIC trial has shown that ruxolitinib is of **benefit second line** in the treatment of PV improved response rates and **significant reduction of symptoms** including itch, fatigue, night sweats, early satiety weight loss and bone pain **[5.2]**, while in ET it only helped with disease related symptom control **[5.3].**

Ruxolitinib has been marketed under the brand name Jakafi® (US name)/Jakavi® (elsewhere name). For the twelve months ended December 31, 2019, **net product revenues of Jakafi® were USD1,700,000,000 [5.4]. For the first three quarters of 2020 (finishing in 30 September 2020), net product revenues of Jakafi® were USD1,870,000,000 [5.4].**
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In the multinational trial of vorinostat in MPNs, the treatment was effective but **due to the side effect profile, the company did not take it forward as a treatment option**. This **avoided the costs** of further development, which can be as much as GBP500,000,000. In contrast, as a result of the phase II trial, **givinostat is being developed further**. The Vice President Research and Development of Italfarmaco states that
"*Italfarmaco S.p.A based on the results…of the trials conducted in PV in which Prof McMullin actively worked,* ***decided to continue the development program in givinostat in PV****…A long term Phase II study is currently ongoing in Europe (NCT01761968)"* **[5.5].**

Thus, the group's work on trials in MPNs brings practice-changing benefits to patients with **improvements and rationalisation of therapy**. The data from McMullin's MPN trials contributed to the development and publication of a **new prognostication tool, published in 2018,** which allows patients' clinical, laboratory and molecular data to be entered, resulting in an individual prediction of likely survival and risk of complications at any particular time point **[5.6]**. Commenting on the importance of the prognostication tool, the Editor of the MPN Forum stated that,
"*Classification and Personalized Prognosis in Myeloproliferative Neoplasm, is* ***a landmark document in the history of MPNs****, reminiscent of William Dameshek's "Some Speculations on the Myeloproliferative Syndromes," (Blood, 1951)"* **[5.7].**

Lower Costs for Health Systems
The **MAJIC trial showed that ruxolitinib was not effective second line for the treatment of ET.** As such, this would represent a potential cost saving to the NHS of about **GBP7,000,000**

per year (GBP44,000 per treatment and a conservative estimate of 160 refractory/intolerant high –risk ET patients) (Cost from NICE guidance TA386).

In the primary thrombocythaemia -1 trial **(PT-1)**, the **largest randomised trial in this disorder in the world**; it was shown that hydroxycarbamide chemotherapy **was not of benefit to intermediate risk patients (previously standard practice)**. This **changed practice** so that patients under the age of 60 with no high-risk features **are no longer treated with the cytotoxic hydroxycarbamide** (which causes increased skin cancers and may have a role in progression to acute leukaemia with attendant morbidity, costs and years of life lost). This is also a saving to the NHS **as many patients are spared exposure to a drug which would cause complications requiring further treatment and associated costs [5.8].**

Professor of Haematology and Clinical Director at Guys and St Thomas' Hospitals in London confirmed the benefit to the NHS:

*"**Professor McMullin has been at the forefront of progress nationally and internationally in the understanding of the genetic basis of these disorders** as well as in developing novel approaches to therapy. **She has led, analysed & published enormous clinical trials which have defined and refined treatment approaches**, allowing appropriate risk stratification and actually leading to savings in the NHS drug budget. **She has also been at the forefront of development/approval of novel agents for MPNs**"* **[5.8].**

Development of Treatment Guidelines from Trial Results

The evidence base from the MPN clinical trials was evaluated by various guideline writing groups and is the basis for recommendations in national and international guidelines for patient management. Prof. McMullin has led and contributed to guidance for the management of PV, ET and MF most recently extensively revising and publishing new guidelines for the management of PV and erythrocytosis for the **British Committee for Standards in Haematology [5.9]**.

The guideline for the diagnosis and management of polycythaemia vera was the recipient of the British Journal of Haematology **editors pick Top Guideline 2018**. These guidelines are all open access on the British Society for Haematology website and are extensively used for the management of MPN on a daily basis in the UK and worldwide. Thus, they have a major impact on patient management and are referenced in treatment guidelines in English health trusts *e.g.* in London, Northern Cancer Alliance, West Essex and Merseyside & Cheshire **[5.9].** The guidelines for the diagnosis and management of polycythaemia vera were downloaded over **22,000** times in 2019.

Data from the trials above contributed to the evidence for formulation of the European LeukemiaNet guidelines which are widely used across Europe and beyond by treating clinicians and as the gold standard for response in clinical trials **[5.10].** Prof McMullin was also a member of the group who evaluated the evidence and wrote the guideline.

In summary, the work of the QUB Haematology group in trials of MPNs and related laboratory research has had major impacts on the treatment and management of MPNs.

5. Sources to corroborate the impact

5.1) Northern Ireland Clinical Trials Network can be contacted to verify patient figures

5.2) Harrison C, McMullin MF, Panchal A, Yap C, Fox S, Bishop R, Curto-Garcia N, Coppell J, Laurie J, Garg M, Ewing J, Knapper S, Crowe J, Maung Z, Godfrey A, Panoskaltsis N, Scherber R, Geyer H, Dueck A, Mesa R, Mead A. Ruxolitinib compared with best available therapy for polycythaemia vera patients resistant or intolerant to hydroxycarbamide in MAJIC-An investigator-led randomised trial. Hemaphere (2018) 2(S1) 264-265.

5.3) Harrison CN, Mead AJ, Panchal A, Fox S, Yap C, Gbandi E, Houlton A, Alomam S, Ewing J, Wood M, Chen F, Coppell J, Panoskaltsis N, Knapper S, Ali S, Hamblin A, Scherber R, Dueck AC, Cross NCP, Mesa R, **McMullin MF**. Ruxolitinib versus best available therapy for ET intolerant or resistant to hydroxycarbamide in a randomised trial. Blood 2017 130(17):1889-1897 PMID: 29074595, cited by 60 (May 2020).

5.4) Jakafi net revenue figures. Incyte Financial Report Q4 2019 (pdf) and 2020

5.5) Testimonial from Vice President Research and Development Italfarmaco S.p.A

5.6) Grinfeld J, Nangalia J, Baxter EJ, Wedge DC, Angelopoulos N, Cantrill R, Godfrey AL, Papaemmanuil E, Gundem G, Maclean C, Cook L, O'Neill L, O'Meara S, Teague JW, Butler AP, Massie CE, Williams N, Nice FL, Andersen CL, Hasselbalch HC, Guigielmelli P, **McMullin MF**, Vannucchi AM, Harrison CN, Gerstung M, Green AR, Campbell PJ. Classification and personalized prognosis in myeloproliferative neoplasms. New England Journal of Medicine 2018: 379(15): 1416-1430. PMID: 30304655, cited by 106 (May 2020).

5.7) Article on the prognostication tool by, editor MPN Forum https://web.archive.org/save/https://mpnforum.com/at-last-a-genetic-atlas-of-mpn-prognostic-mutations/

5.8) Testimonial from Clinical Director at Guys and St Thomas' Hospitals London

5.9) MPN Treatment Guidelines authored by MF and published by British Society for Haematology. Also citation of these guidelines by English Health Trusts (London Guidelines for Polycythaemia Vera, Pan-London Haemato-Oncology Clinical Guidelines, Merseyside and Cheshire NHS Guidelines for diagnosis and management of adult myeloproliferative neoplasms, Haematology Cancer Clinical Guidelines Haematology Expert Advisory Group (EAG) on behalf of Northern Cancer Alliance, West Essex Clinical Commissioning Group Guidance on Hydroxycarbamide for Myeloproliferative Neoplasms)

5.10) Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, Verstovsek S, Mesa R, Kiladjian JJ, Hehlmann R, Reiter A, Cervantes F, Harrison C, **McMullin MF**, Hasselbalch HC, Koschmieder S, Marchetti M, Bacigalupo A, Finazzi G, Kroeger N, Greisshammer M, Birgegard G, Barosi G. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet, cited by 120 (May 2020).