**Institution:**
Cardiff University

**Unit of Assessment:**
UoA1

**Title of case study: Cardiff-led research underpins new UK and International clinical treatment guidelines for the management of acquired haemophilia A**

## 1. Summary of the impact

A Cardiff researcher has led an International 15 year programme resulting in multiple novel findings which have led to changes in the recommended diagnosis and treatment of acquired haemophilia A (AHA). The research has, for the first time, allowed the comparison of immunosuppressive regimens for inhibitor eradication and comparison of the efficacy of treatment strategies to control bleeds. Studies led directly to the production of UK and International guidelines on the management of AHA with 14 of the 18 specific recommendations in the UK guideline being underpinned by Cardiff-led research.

## 2. Underpinning research

AHA is an autoimmune disease caused by antibodies to clotting factor VIII. It mainly affects older people with an incidence of 1.5/million/year. It may be precipitated by underlying autoimmune disease, malignancy or pregnancy. AHA is associated with severe bleeding and 30-40% one year mortality.

Before the Cardiff-led research programme, the description of AHA was limited to single centre cohorts and collections of referral centre experiences, reflecting only the more severely affected patients. This information was not applicable to most patients. Studies had short follow-up and long-term outcomes were unknown. There was only one controlled study in the field and this was underpowered and uninformative. Management guidelines therefore relied on expert opinion rather than evidence.

To define standards of care for AHA based on evidence, the Cardiff team, led by by Dr John Giddings (Lecturer and Senior Lecture, Cardiff University, 1972 -2007) and Peter Collins (Cardiff and Vale, NHS consultant until he became Cardiff University Senior Lecturer 2001-2010, Reader in Haematology 2010-2013 and since promoted to Clinical Professor), initiated a programme of studies in 1996, which evolved into UK and Europe-wide collaborations.

### The All Wales AHA cohort

An All-Wales study was designed to establish the incidence and long term outcome of AHA in a well defined, unbiased cohort of patients between 1996 and 2002[3.1]. This established the platform for Cardiff University to design and lead a prospective UK-wide surveillance study.

### UK AHA surveillance study

The UK study was initiated and led by Collins in Cardiff and documented the first complete description of AHA and its treatment in an unbiased cohort of patients. The unique and outstanding strength of the UK study is that all UK Hospitals reported on all patients presenting with AHA over a two-year period (2001-2003), generating a national cohort free from recruitment or reporting bias. The study established the incidence, predisposing conditions, age distribution and long-term outcomes of patients with AHA and is recognised as the definitive publication in the field[3.2].

### The European Acquired Haemophilia Registry (EACH2)

In rare diseases prospective randomised trials are challenging and so Cardiff established a European collaboration (co-chaired by Collins) designed to investigate the optimal treatment of AHA. Involving 93 centres from 13 countries, this study recruited between 2003 and 2009 and included about 14% of European patients during that time. Propensity score matching allowed comparison of treatment outcomes.

World-first findings of this three stage research program were:

1. The age-related incidence of AHA and the incidence in pregnancy[3.1,3.2,3.6]
2. The disease characteristics and underlying conditions in unselected populations and the effect of these on long-term outcomes[3.1,3.2,3.3]
3. Evidence for significant diagnostic delay and lack of awareness of the implications of

abnormal coagulation results amongst clinicians that puts patients at unnecessary risk of severe bleeding[3.3]
4. That fatal bleeding may occur up to 6 months after presentation even if the initial presentation appears benign[3.2]
5. The remission rate and survival associated with different immunosuppressive therapies in matched cohorts of patients. The combination of steroids and cyclophosphamide was shown to be associated with an improved remission rate compared to steroids alone. Regimens using rituximab conferred no additional benefit, contrary to previously held opinion and practice[3.4]
6. Significant morbidity and mortality associated with immunosuppressive regimens[3.2,3.4]
7. The high incidence of relapse (10-20%) after stopping immunosuppression[3.2,3.4]
8. The two inhibitor bypassing agents, licensed to treat bleeding in AHA, are equally effective for controlling bleeding and both are better than factor VIII[3.5]
9. There is a high incidence of serious thrombotic side effects associated with the use of bypassing agents in patients with AHA[3.5]
10. Between 25 and 30% of bleeds resolved without haemostatic treatment and a description of the characteristics of these self-limiting bleeds[3.2,3.4]

These findings were used to produce the first evidence-based treatment guidelines in the field.[5.2-5.4]

**3. References to the research**

3.1. **Collins P**, **Macartney N**, **Davies R**, **Lees S**, **Giddings J** and Majer R. (2004) A population based, unselected, consecutive cohort of patients with acquired haemophilia A. *Br J Haematol* 124:86-90. DOI: 10.1046/j.1365-2141.2003.04731.x

3.2. **Collins P**, Hirsch S, Baglin T, Dolan G, Hanley J, Makris M, Keeling D, Liesner R, Brown S, Hay C. (2007) Acquired haemophilia A in the UK: a two year national surveillance study by UK Haemophilia Centre Doctors' Organisation. *Blood* 109:1870-1877. DOI:10.1182/blood-2006—06-029850.

3.3. Knoebl P, Marco P, Baudo F, **Collins PW**, Huth-Kühne A, Nemes L, Pellegrini F, Tengborn L, Lévesque H. (2012) Demographic and clinical data in acquired hemophilia A: Results from the European Acquired Haemophilia (EACH2) Registry. *J Thromb Haemostas* 10:622-631. DOI: 10.1111/j.1538-7836.2012.04654.x

3.4. **Collins P**, Baudo F, Knoebl P, Lévesque H, Nemes H, Pellegrini F, Marco P, Tengborn L, Huth-Kühne A, (2012) Immunosuppression for acquired hemophilia A: Results from the European Acquired Haemophilia Registry (EACH2). *Blood* 120:47-55. DOI:10.1182/blood-2012-02-409185

3.5. Baudo F, **Collins P**, Huth-Kuehne A, Lévesque H, Marco P, Nemes L, Pellegrini F, Tengborn L, Knoebl P. (2012) Management of Bleeding in Acquired Haemophilia A: Results from the European Acquired Haemophilia (EACH2) Registry. *Blood* 120:39-46. DOI :10.1182/blood-2012-02-408930

3.6. Tengborn L, Baudo F, Huth-Kühne A, Knoebl P, Lévesque H, Marco P, Pellegrini F, Nemes L, **Collins P**. (2012) Pregnancy-associated acquired haemophilia A: Results from the European Acquired Haemophilia (EACH2) Registry. *British Journal of Obs and Gynae* 119:1529-1537. DOI: 10.1111/j.1471-0528.2012.03469.x

**4. Details of the impact**

The Cardiff-led programme has defined the standard of care for AHA internationally. This is evidenced by the new national[5.2] and international[5.3,5.4] treatment guidelines for AHA that have been written (led by Collins in Cardiff with Angela Huth-Kuhne in Germany), based on novel data generated by Cardiff-led research[3.1-3.6], that for the first time allow evidence-based treatment of AHA.

Our All-Wales[3.1] and UK[3.2] studies initiated this process prior to the REF impact period, forming the basis of UK national guidelines in 2006[5.1] (150 citations). Missing information in the 2006 guidelines was:

1. Data about the relative efficacy of available immunosuppressive regimens to eradicate the factor VIII inhibitors in matched patients

2. Comparison of the efficacy of haemostatic treatments to treat bleeds in matched patients.

3. Information about the high frequency of diagnostic delay.

4. Information about the incidence of thrombotic complications of haemostatic agents

Over the REF period, further data from the European study[3.3-3.6] led to the UK guidelines being substantially changed and updated in 2013[5.2], a process co-ordinated by The UK Haemophilia Centre Directors' Organisation (UKHCDO) Inhibitor Working Party chaired by Collins of Cardiff University. These guidelines have been endorsed by the British Committee on Standards in Haematology, UKHCDO and British Society of Haematology. Of the 18 specific management recommendations on AHA in the 2013 guideline[5.2], 14 are underpinned by evidence produced by the Cardiff-led research programme. The guidelines have been agreed and adopted by the English Specialised Commissioning Group (The Haemophilia Clinical Reference Group) which has directed that all 90 UK haemophilia centres must follow UKHCDO guidelines.

The Cardiff-led research programme has also resulted in the production of two international guidelines[5.3,5.4] as collaborations between Cardiff University and European, north American and Japanese colleagues. These guidelines have been adopted worldwide and are the most cited papers in the field since 2009 (90 citations); they have been cited by groups from Europe, north and south America, India, Korea and Japan as accepted standard practice.

**Recommendations in clinical guidelines and treatment protocols based on Cardiff-led research**

**RECOGNITION AND DIAGNOSIS**

1. Novel finding: Significant diagnostic delay is common even after abnormal clotting tests have been found (European study)[3.3]
New treatment recommendation: Laboratories should investigate abnormal clotting tests for AHA even if the referring clinician had not requested them and haematologists should directly inform clinicians of the implications of results[5.2-5.4]

2. Novel finding: Delay in recognition of symptoms of AHA (European study)[3.3]
Action: Typical presentations highlighted in management guidelines aimed at general clinicians[5.2-5.4]

3. Novel finding: Fatal bleeding may occur up to 6 months after diagnosis if inhibitor is not eradicated (UK study)[3.2]
New treatment recommendation: refer to specialist centres to start immunosuppression as soon as the diagnosis is made even if presentation appears benign[5.2-5.4]

**TREATMENT**

4. Novel finding: Combined steroids and cyclophosphamide result in a higher stable remission rate than steroids alone and rituximab confers no additional benefit (European study)[3.4]
New treatment recommendation: Recommended first line immunosuppression protocol changed between the 2006 and 2013 UK guidelines and rituximab to be reserved for second line therapy.[5.2]

5. Novel finding: There is a high incidence of relapse after immunosuppression has been stopped (UK and European studies)[3.2,3.4]
New treatment recommendation: Longer (at least one year) and more intensive follow up is required in specialist clinics[5.2-5.4]

**SAFETY**

6. Novel finding: There is significant morbidity and mortality associated with immunosuppressive regimens (UK and European studies)[3.2,3.4]
New treatment recommendation: Immunosuppressive protocols adapted to take the age and co-morbidity of patients into account[5.2-5.4]

7. Novel finding: The two available inhibitor bypassing agents are equally as effective for controlling bleeds but both are better than factor VIII (European study)[3.5]
New treatment recommendation: Bypassing agents should be used as first line therapy to treat bleeds.[5.2-5.4]

8. Novel finding: Iatrogenic bleeding is common following venepuncture, blood pressure monitoring

and invasive procedures. (UK study)[3.2]
New treatment recommendation: Venepuncture and blood pressure monitoring should be kept to a minimum and invasive procedures postponed until factor VIII level has increased.[5.2-5.4]

9. Novel finding: There is a high incidence of arterial and venous thrombotic side effects associated with treating AHA with bypassing agents (European study)[3.5]
New treatment recommendation: Bypassing agents should only be used on the advice of specialist haemophilia centres. Bypassing agents in AHA should not be used in combination or in high dose regimens licensed for congenital haemophilia[5.2-5.4]

10. Novel finding: 25-30% of bleeds resolved without haemostatic treatment and these bleeds have characteristic features (UK and European studies)[3.2,3.3,3.5]
New treatment recommendation: Withhold bypassing agents in certain types of bleeds to limit the risk of thrombotic complications.[5.2-5.4]

**Effect of research on measures of clinical outcomes**
The treatment guidelines have been disseminated to patient groups, clinicians specialising in haemostasis and general physicians around the world. By ensuring they receive the most appropriate treatment and care, the recommendations impact on all patients with AHA. The international guideline published in 2009, aimed at specialist haematologists working in tertiary referral centres, has been cited by groups from Europe, north and south America, India, Korea and Japan as accepted standard practice.

**5. Sources to corroborate the impact**

5.1. Hay C, Brown S, **Collins P**, Keeling D, Liesner R. (2006) The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol*. 133:591-605. DOI: 10.1111/j.1365-2141.2006.06087.x (Shows guidelines included prior to research)

5.2. **Collins P**, Chalmers E, Hart D, Jennings I, Liesner R, Rangarajan S, Talks K, Williams M, Hay. (2013) Diagnosis and management of acquired coagulation factor inhibitors: a guideline from UKHCDO. *Brit J Haematol*. 162:758-73, 2013. DOI: 10.1111/bjh.12463 ((Backs up claim of creation of new guidelines)

5.3. **Collins P**, Baudo F, Huth-Kühne A, Ingerslev J, Kessler C, Mingot Castellano M, Shima M, St-Louis J, Lévesque H. (2010) Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. *BMC Research Notes* 3:161 doi:10.1186/1756-0500-3-161 (Backs up claim of new treatment recommendation)

5.4. Huth-Kuhne A, Baudo F, **Collins P**, Ingerslev J, Kessler CM, Levesque H, Castellano ME, Shima M, St-Louis J. (2009) International recommendations on the diagnosis and treatment of patients with acquired haemophilia A. *Haematologica* 94:566-575. doi: 10.3324/haematol.2008.001743 (Backs up claim of inclusion in international guidelines and new treatment recommendations)

Suggested expert external referees who will confirm that 2013 UK treatment guidelines were based on data derived from Cardiff University research are:

1. Chair of UK Haemophilia Centre Doctors' Organisation

2. Chair of the Haemostasis and Thrombosis Taskforce of the British Committee for Standards in Haematology