Clinical Commissioning Policy Proposition:

Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages)

Reference: NHS England 1819 / NICE ID014

Contents

1   Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

See also, section 4 for additional definitions of terms used in this document.

About haemophilia A

Haemophilia A is a rare condition that affects the blood's ability to clot. Haemophilia A is usually inherited and usually occurs in males. Instances of haemophilia in females are rare.

Normally, when a person cuts themselves, substances in the blood called clotting factors combine with blood cells called platelets, making the blood clot and stopping the bleeding. People with haemophilia A do not have enough of a clotting factor called factor VIII (eight) in their blood, or it isn't working properly. This means they cannot form strong clots and so they bleed for longer than usual.

Symptoms of haemophilia A can be mild to severe, depending on the person's level of clotting factor VIII. People with haemophilia A may bruise easily and bleed for longer than people who do not have haemophilia A. Bleeding can be external (for example, from cuts) or internal (for example, into the brain or into joints, including the ankle, knee and elbow) and can be caused by trauma or develop spontaneously.

Bleeding into joints causes acute pain and over time irreversible damage to the joints (reducing the person's ability to move) and reduce the person's quality of life. Bleeding into the brain may be fatal.

People with haemophilia A are currently treated by replacing the missing factor VIII. Factor VIII replacement treatment prevents bleeds and allows the person to grow up with normal joints.

About current treatments

There is currently no cure for haemophilia A. Lifelong treatment is required. The aim of treatment for haemophilia A is to prevent bleeding episodes from occurring. In particular, the aim is to prevent joint bleeds (and therefore prevent joint damage) and other serious bleeds which can lead to disability and death. Bleeds can be prevented or reduced by injections of factor VIII into the vein (either directly or via a central venous access device for patients who require it), given every 2 to 3 days. If a bleed occurs, it is treated with injections of factor VIII.

About the new treatment

Emicizumab is a drug used to prevent bleeding or reduce the number of bleeds in people with haemophilia A. Emicizumab works by mimicking the action of factor VIII. Emicizumab binds to factor X (ten) and activated factor IX (nine) which brings those clotting factors near each other and activates the blood clotting system even if no factor VIII is present. This is different to how replacement factor VIII works. Emicizumab is injected under the skin (subcutaneous injection). When a person starts on emicizumab they need to inject it once a week for the first 4 weeks (this is called a loading dose). After this, the person can inject emicizumab either once a week, once every 2 weeks or once every 4 weeks. The dose given depends on the patient's weight.

What we have decided

NHS England has carefully reviewed the evidence to prevent or reduce the frequency of bleeding episodes in people with severe haemophilia A who do not have factor VIII inhibitors with emicizumab. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether emicizumab will be routinely commissioned for this indication will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

People with haemophilia A have deficient clotting factor VIII activity, placing them at risk of spontaneous and traumatic bleeding events. Regular replacement of the missing factor VIII every 2 to 3 days to prevent bleeds is the standard of care for people with severe haemophilia A.

Emicizumab works by linking activated factor IX and factor X to activate the blood clotting system in the absence of factor VIII.

4 Definitions

Antibody	A type of protein produced by the body's immune system, which combines with foreign material in the body (such as bacteria or viruses) to act against it
Bethesda units	The Bethesda assay is used to quantify the concentration of factor VIII inhibitor. One Bethesda unit (BU) is the amount of inhibitor required to neutralise 50% of a unit of factor VIII in normal plasma after incubation at 37°C for 2 hours
Central venous access device	A catheter that is inserted into the central venous system with the internal tip sitting within the superior/inferior vena cava or right atrium. This allows the administration of

	fluids, blood products, medication and other therapies into the bloodstream.
Factor VIII	A protein involved in blood clotting
Haemophilia A	An inherited condition, affecting predominately males, in which there is excessive bleeding which can follow trauma or can occur spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein
Inhibitor	An antibody produced by the immune system which neutralises and de-activates factor VIII
Inhibitor titres	Measured in Bethesda units (BU). The higher the number of Bethesda units, the more inhibitors are present
Target joint	A joint in the body where there have been at least 3 bleeds in the last 6 months
Titre	The concentration of a substance (such as an antibody) in solution, which is worked out by a method called titration

5 Aims and Objectives

This policy proposition considered: emicizumab as prophylaxis in people with congenital haemophilia A without factor VIII inhibitors (all ages).

The objectives were to:

- ensure evidence based commissioning with the aim of improving outcomes for patients with haemophilia A without factor VIII inhibitors; and
- identify clinical criteria for treating patients with haemophilia A without factor VIII inhibitors.

6 Epidemiology and Needs Assessment

The UK National Haemophilia Database Bleeding Disorder Statistics for April 2016 to March 2017 reports that there are approximately 6,478 people in the UK with mild, moderate or severe forms of haemophilia A (not including low-level carriers; factor VIII level ≥40 IU/dL). For England only, 5,205 people do not have inhibitors to factor VIII. Of these people 1,419 people have severe haemophilia.

The eligible patient population for emicizumab in England is considered to be equivalent to the patients with severe haemophilia A without current inhibitors (n=1,419).

Permanent joint damage: About 90% of people with severe haemophilia experience damage in major joints that is irreversible and rapidly progressive in the absence of treatment. This is called haemophilic arthropathy and is one of the main challenges in managing haemophilia A. These changes often happen in one to six joints (ankles, elbows, knees). Joint damage starts at a young age and usually becomes clinically significant when the person is in their teens or 20s (O'Hara et al., 2017).

Method of administration: Factor VIII must be given intravenously, which can cause pain and stress, and requires frequent access to veins: this may be difficult for some patients to maintain long-term. As a result, children with haemophilia A often require central venous access devices (CVADs) to be inserted surgically, requiring a hospital stay of around 5 days. CVADs allow easier treatment administration of intravenous factor VIII, but patients and carers need to be trained how to use them, and having a CVAD increases the risk of infection and thrombosis (Rodriguez et al., 2015). Repeated intravenous injections can damage veins, making venous access more difficult. Because of this some people with haemophilia A may require an arteriovenous fistula to administer factor VIII. Emicizumab is administered subcutaneously, removing the need for venous access.

Dose frequency: Factor VIII has a relatively short half-life, and requires injections into veins every 2-3 days to prevent bleeds and up to every 8 to 12 hours to treat bleeds. Emicizumab has a long half-life and is administered once a week, once every 2 weeks or once every 4 weeks. Less frequent administration may increase adherence to prophylactic treatment and which may improve overall bleeding control. Patients will also need to carry fewer doses of prophylactic treatment when away from home for extended periods of time.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

The evidence for the efficacy and safety of emicizumab came from 1 study that was included in the clinical evidence review.

[Mahlangu et al. 2018 (HAVEN 3)](#) was a 24-week, open-label, randomised controlled trial (RCT) in 152 people (89 randomised and 63 non-randomised) with severe haemophilia A without factor VIII inhibitors (median age 38 years [range 13 to 77]; 5.3% aged less than 18 years).

Effectiveness

Bleeding outcomes

The primary efficacy outcome in Mahlangu et al. (2018) was the difference in the rate of treated bleeding events over at least 24 weeks in people previously treated with on-demand factor VIII, reported as an annualised bleeding rate. Significantly lower annualised bleeding rates were seen in participants treated with emicizumab 1.5 mg/kg every week (group A; 1.5 events, 95% CI 0.9 to 2.5) and with emicizumab 3.0 mg/kg every 2 weeks (group B; 1.3 events, 95% CI 0.8 to 2.3) compared with no prophylaxis (group C; 38.2 events, 95% CI 22.9 to 63.8). The annualised bleeding rate was 96% lower in group A and 97% lower in group B, compared with no prophylaxis, p<0.001 for both comparisons.

Similar results were reported for all secondary bleeding outcomes in the trial, with both emicizumab groups having significantly lower annualised bleeding rates compared with no prophylaxis for: all bleeding events, spontaneous bleeding events, joint bleeding events and target-joint bleeding events

Health-related quality of life

Health-related quality of life was reported using the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale score. The Haem-A-QoL can assess health-related quality of life in people with haemophilia A and B, and consists of 46 items, composed of 10 subscales. Subscale scores are transformed to a 0 to 100 scale, with lower scores suggesting better health-related quality of life. A reduction of 10 points on the physical health subscale represent a clinically meaningful improvement in health-related quality of life ([Wyrwich et al. 2015](#)).

The adjusted mean difference in Haem-A-QoL physical health subscale score between group A and group C was 12.5 points (95% CI −2.0 to 27.0, p=0.09, not statistically significant). The adjusted mean difference between group B and group C was 16.0 points (95% CI 1.2 to 30.8, considered non-significant due to the order of the outcomes in the hierarchical testing framework).

There was no statistically significant difference in Haem-A-QoL physical health subscale score between either emicizumab group (group A or B) and the no prophylaxis group (group C).

Patient preference

Patient preference for treatment was an exploratory end point, assessed using the EmiPref patient survey. It would appear that this survey had been developed for this study and has not been externally validated.

In total, 95/134 participants (71%) completed the EmiPref survey, with 94% (95% CI 87 to 98) preferring emicizumab, and 45/46 participants in group D (98%, 95% CI 88 to 100) favouring emicizumab over factor VIII prophylaxis.

Before-and-after comparison

Mahlangu et al. (2018) reported intra-individual comparisons of emicizumab prophylaxis with factor VIII prophylaxis in a sub-set of participants previously recruited in a non-interventional cohort study (Kruse-Jarres et al., 2019). The non-interventional study collected real-world data on bleeding rates, health-related quality of life and safety in people being treated according to routine clinical practice.

The people in group D who had taken part in the non-interventional study (n=48) had a significantly lower annualised treated bleeding rate on emicizumab prophylaxis (1.5 events, 95% CI 1.0 to 2.3) compared with factor VIII prophylaxis (4.8 events, 95% CI 3.2 to 7.1), equating to a 68% reduction in bleeding rate (rate ratio [RR] 0.32, 95% 0.20 to 0.51, p<0.001).

While receiving factor VIII prophylaxis during the non-interventional study, 40% of participants had no bleeding events, compared with 54% of the same participants treated with emicizumab in the study by Mahlangu et al. (2018).

Results of such intra-individual comparisons should be interpreted with caution, particularly when comparing results of real-world observational studies with the results of more rigidly controlled clinical trials. Participants in the real-world, non-interventional study were treated according to local routine clinical practice, and as such there may have been important differences in how patients were managed between centres (Kruse-Jarres et al., 2019). Adherence to prophylactic factor VIII was variable in the non-interventional study, with around two-thirds of participants taking ≥80% of doses and one-third taking <80% of doses. Sub-optimal adherence to prophylactic factor VIII may account for the higher bleeding rate observed in the non-interventional study (Kruse-Jarres et al., 2019). It is also unclear how participants were selected from the real-world, non-interventional study, and selection bias may be present.

However, the authors of Mahlangu et al. (2018) state that intra-individual comparisons are appropriate because they control for person-related confounders; and such comparisons are particularly suitable for rare, stable diseases (such as haemophilia A) and for interventions without a carryover effect (factor VIII). They also state that the median annualised bleeding rate seen in the non-interventional study (1.8 events) was similar to that seen in prospective studies of prophylaxis with factor VIII (range 0.9 to 4.1 events).

The results of this study suggest that emicizumab may be as least as effective as real-world factor VIII prophylaxis. However, it must be acknowledged that emicizumab has not been compared adequately with optimised standard FVIII replacement treatment.

Safety and tolerability

Adverse events

In total, 543 adverse events were reported in 127/150 participants (85%) who received emicizumab prophylaxis in the study by Mahlangu et al. (2018). The most

common adverse events were injection-site reaction (reported in 25% of participants), arthralgia (joint pain; 19%) and nasopharyngitis (12%). Fourteen serious adverse events were reported, including bleeding events, a cardiac disorder and infections. No serious adverse events were considered by the investigators to be related to emicizumab treatment.

There were no deaths, no cases of thrombotic microangiopathy and no thrombotic events.

One person stopped treatment with emicizumab due to a number of adverse events (including insomnia, alopecia, nightmares, lethargy and headache) that were considered to be related to emicizumab.

In total, 215 events of co-exposure to emicizumab and factor VIII occurred in 64 participants, with 43 events involving an average dose of factor VIII of at least 50 IU/kg per day and 8 events lasting 24 hours or longer. There were no serious adverse events related to co-exposure to emicizumab and factor VIII.

No new factor VIII inhibitors developed in participants receiving emicizumab. One participant had undergone immune tolerance induction (ITI) in 1987 and had a history of intermittent detectable inhibitors. This person had re-emergence of a detectable inhibitor at week 13 (1.6 Bethesda units, and this was still detectable at 0.7 Bethesda units at week 25.

Pharmacokinetics and antibodies

No participants developed antibodies to emicizumab during the study by Mahlangu et al. (2018). The SPC for emicizumab states that 4 participants (2.1%) in the phase I/II clinical trials tested positive for anti-emicizumab antibodies, all of which were non-neutralising.

8 Proposed Criteria for Commissioning

NHS England will routinely commission emicizumab prophylaxis in adults and children with severe congenital haemophilia A (defined as factor VIII level

<1 IU/dL, or <1% of normal) without current inhibitors to prevent bleeding episodes.

The UKHCDO will provide a dosing algorithm which all prescribers will comply with. The algorithm is designed to:

- Minimise the volume which patients will be required to inject
- Minimise the risk of dosing errors
- Minimise drug waste from each vial, so that when selecting the maintenance dose regimen for each patient the frequency may be adjusted to weekly, every 2 weeks or every 4 weeks. Doses will be determined by the patient's weight as per the licensed indications.

Emicizumab will only be commissioned and funded via Haemophilia Comprehensive Care Centres and a Prior Approval Funding request must be submitted for each case. The restriction to Haemophilia Comprehensive Care Centres will be reviewed within a period not exceeding 24 months from policy commencement. Haemophilia centres with eligible patients should refer those patients to their linked Haemophilia Comprehensive Care Centre and the Haemophilia Comprehensive Care Centre will commission the treatment. Once treatment has been initiated the patient's treatment may be routinely managed by their Haemophilia Centre but should be reviewed annually by the Haemophilia Comprehensive Care Centre.

Patients, or their carers, must be trained in the storage, handling and administration of emicizumab and satisfy clinical teams of their competence in these respects. Patients will receive their medication via an approved homecare service and must comply with the requirements of the service.

When emicizumab is initiated patients should be advised to identify the emergence of any delayed allergic reactions or injection site reactions.

In common with any prophylaxis regimen in the management of haemophilia A, patients on emicizumab are also at risk of traumatic bleeds and will continue to possess a small quantity of factor VIII at home for the self-management of bleeds.

As with current practice, patients, or their carers, will be counselled routinely on the recognition and management of bleeds and the need for clinical advice.

Patients, or their carers, must provide their clinical team with data pertaining to dose administration and related clinical sequelae such as bleeding episodes. This is most easily achieved through the use of a secure therapy recording digital interface, such as Haemtrack™.

During treatment

Bleeding episodes which occur during treatment with emicizumab must be managed by a Haemophilia Comprehensive Care Centre that has facilities for 24 hour in-patient care for managing bleeding episodes or at local Haemophilia Centres if treatment is commissioned, initiated and monitored by a Haemophilia Comprehensive Care Centre (see above).

Patients on long term prophylaxis should have their regimens reviewed at least every 6 months.

Patients should have their factor VIII inhibitor levels tested every 12 months by an appropriate technique that enables the detection of inhibitors even in the presence of emicizumab. If a patient using emicizumab prophylaxis requires factor VIII treatment for a bleed, they must be monitored regularly for inhibitors after the use of FVIII if they have had less than 50 exposure days to FVIII.

Patients and clinicians should be advised that the following tests are affected by the presence of emicizumab:

- Activated partial thromboplastin time (aPTT)
- Bethesda assays (clotting-based) for FVIII inhibitor titres
- One-stage, aPTT-based, single-factor assays
- aPTT-based Activated Protein C Resistance (APC-R)
- Activated clotting time (ACT)

Clinicians will need to conduct alternative tests if any of these parameters are required. All surgery and all major bleeds in non-inhibitor haemophilia patients receiving emicizumab prophylaxis should be managed through a Haemophilia

Comprehensive Care Centre with 24-hour access to a bovine chromogenic FVIII assay.

Patients will not normally hold or possess more than 3 months of medication at any one time.

Stopping Criteria:

After 6 to 12 months treatment with emicizumab, it should be withdrawn and ceased in the following situations:
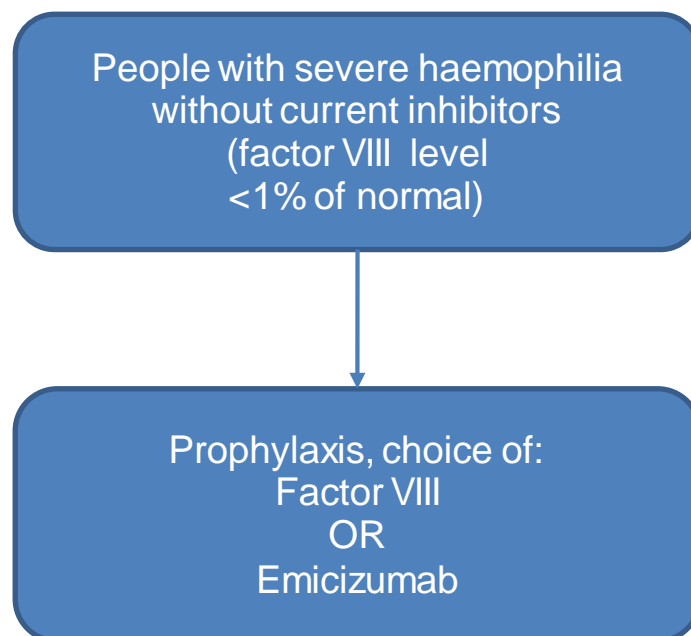
- Where there is an annualised bleeding rate of 5 or more spontaneous bleeds or bleeds related to activities of daily living compared with the patient's baseline bleeding rate over the 12 months preceding emicizumab when treated with intravenous factor VIII.
  - For patients who are treatment naïve, where there is an annualised bleeding rate of 5 or more spontaneous bleeds or bleeds related to activities of daily living.
- Loss of efficacy due to the development of antibodies to emicizumab, or as otherwise clinically determined.
- Treatment with emicizumab should be withdrawn and ceased immediately in the case of a severe allergic reaction.

The decision to continue with treatment in the following situations must be undertaken by an appropriate Haemophilia MDT to balance the risks and benefits:

- An occurrence of a thrombotic event or other significant adverse reaction or any major comorbidity arises or is identified during treatment
- Neutralising antibodies to emicizumab are identified

9   Proposed Patient Pathway

Current treatment options are prophylactic or episodic treatment with factor VIII (either factor VIII or enhanced half-life factor VIII), the choice of which is guided by disease severity and bleeding history.

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┌─────────────────────────────────┐
│   People with severe haemophilia│
│   without current inhibitors     │
│   (factor VIII level             │
│   <1% of normal)                 │
└─────────────────────────────────┘
              │
              ▼
┌─────────────────────────────────┐
│   Prophylaxis, choice of:        │
│   Factor VIII                    │
│   OR                             │
│   Emicizumab                     │
└─────────────────────────────────┘
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10 Proposed Governance Arrangements

Each provider organisation treating children with a medicine approved under this policy will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place.

Provider organisations must register all patients using software to monitor bleeds (a secure therapy recording system) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Treatment with emicizumab should be initiated and monitored under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders at a haemophilia comprehensive care centre (or at haemophilia centres under the direction and coordination of a haemophilia comprehensive care centre).

11 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team. Emicizumab is listed as a tariff-exempt medicine.

12 Proposed Audit Requirements

All patients must be registered with the UK National Haemophilia Database. The outcome of emicizumab prophylaxis must be reported to the National Haemophilia Database annually. Patients receiving emicizumab must record all their bleeds and treatment on a secure therapy recording system.

All haemophilia comprehensive care centres will be required to participate in an ongoing national audit which will include:

- Starting dose and dose changes to review compliance with protocols
- Cardiovascular risk factors and history when commencing emicizumab
- Factor VIII usage
- Number of bleeding episodes per year (and annualised baseline number of bleeding episodes before commencing emicizumab prophylaxis)
- Haemophilia Joint Health Score (HJHS)
- Adverse reactions (including thrombotic events and allergic reactions)
- Results from testing for factor VIII inhibitors for all patients

In addition, data will be collected from NHS England's Prior Approval Request forms which will inform commissioners about prior treatment modalities and other important baseline treatment parameters.

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition include a review of the clinical evidence available for emicizumab and the following:

Health Service Guidance HSG (93) 30 'Provision of Haemophilia Treatment and Care'.

NHS England (2013) 2013/14 NHS Standard Contract for Haemophilia (All Ages) (B05/S/a).

NHS England (2016) CQUIN for 2017 - 2019

Additional evidence sources are listed in the table of references below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Alliance, H. (2006) *A National Service Specification for Haemohilia and Other Inherited Bleeding Disorders* [Online]. Available: http://www.ukhcdo.org/docs/HaemAlliance-NatSvsSpec2006.pdf (accessed Nov 2018).

Blanchette, V. S., Key, N. S., Ljung, L. R., Manco-Johnson, M. J., Van Den Berg, H. M., Srivastava, A., Subcommittee On Factor VIII, F. I. X., Rare Coagulation Disorders of the, S., Standardization Committee of the International Society on, T. & Hemostasis (2014) Definitions in hemophilia: communication from the SSC of the ISTH. Journal *of* Thrombosis and Haemostasis 12**:** 1935-9.

Brown, T. M., Lee, W. C., Joshi, A. V. & Pashos, C. L. (2009) Health-related quality of life and productivity impact in haemophilia patients with inhibitors. Haemophilia*,* 15**:** 911-7.

Hanley, J., Mckernan, A., Creagh, M. D., Classey, S., Mclaughlin, P., Goddard, N., Briggs, P. J., Frostick, S., Giangrande, P., Wilde, J., Thachil, J., Chowdary, P. & Musculoskeletal Working Party of the, U. (2017) Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline. Haemophilia 23**:** 511-520.

Keeling, D., Tait, C. & Makris, M. (2008) Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. Haemophilia 14**:** 671-84.

Kruse-Jarres, R., Oldenburg, I.., Santagostino, E., Shima, M., Kempton, C.L., Kessler, C.M., Lehle, M., Chebon, S., Selak Bienz, N., Asikanius, E., and Mahlangu, J. (2019) Bleeding and safety outcomes in persons with haemophilia A without inhibitors: Results from a prospective noninterventional study in a real-world setting. Haemophilia 2019;1–8. DOI: 10.1111/hae.13655

Mahlangu J, Oldenburg I, Paz-Priel C et al. (2018) Emicizumab prophylaxis in patients who have hemophilia A without Inhibitors. New England Journal of Medicine 379(9): 811-822

Morfini, M., Haya, S., Tagariello, G., Pollmann, H., Quintana, M., Siegmund, B., Stieltjes, N., Dolan, G. & Tusell, J. (2007) European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 13**:** 606-12.

NHS England (2013). NHS standard contract for haemophilia (all ages) B05/S/a. [Online]. https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-haemophilia.pdf (accessed Nov 2018).

NHS England (2016) Revised specialised commissioning CQUINs 2016-17 2017-18. [Online].https://www.england.nhs.uk/wp-content/uploads/2016/11/pss-cquin-schemes.pdf (accessed Nov 2018).

NHS England (2016) NHS England. Manual for prescribed specialised services 2016-17*.* https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf (accessed Nov 2018).

O'hara, J., Hughes, D., Camp, C., Burke, T., Carroll, L. & Diego, D. G. (2017) The cost of severe haemophilia in Europe: the CHESS study. Orphanet Journal of Rare Diseases 12: 106.

Richards, M., Williams, M., Chalmers, E., Liesner, R., Collins, P., Vidler, V., Hanley, J. & Paediatric Working Party Of The United Kingdom Haemophilia Doctors, O. (2010) A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. British Journal of Haematology 149**:** 498-507.

Rodriguez, V., Mancuso, M. E., Warad, D., Hay, C. R., Dimichele, D. M., Valentino, L., Kenet, G. & Kulkarni, R. (2015). Central venous access device (CVAD) complications in Haemophilia with inhibitors undergoing immune tolerance induction: Lessons from the international immune tolerance study. Haemophilia*,* 21**:** e369-74.

Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., Key, N. S., Kitchen, S., Llinas, A., Ludlam, C. A., Mahlangu, J. N., Mulder, K., Poon, M. C., Street, A. & Treatment Guidelines Working Group on behalf of the World Federation of, H. (2013) Guidelines for the management of hemophilia. Haemophilia, 19: e1-47.

UKHCDO National Haemophilia Database. (2016) Bleeding Disorder Statistics for 2015-2016 [Online]. http://www.ukhcdo.org/wp-content/uploads/2017/03/Bleeding-Disorder-Statistics-for-April-2015-to-March-2016-for-UKHCDO-Website.pdf (accessed Nov 2018).

White, G. C., 2nd, Rosendaal, F., Aledort, L. M., Lusher, J. M., Rothschild, C., Ingerslev, J., Factor, V. & Factor, I. X. S. (2001) Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thrombosis and Haemostasis 85: 560.

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