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ORIGINAL ARTICLE

Women with bleeding disorders

European principles of care for women and girls with inherited bleeding disorders

Karin van Galen[1] | Michelle Lavin[2] | Naja Skouw-Rasmussen[3] | Kathelijn Fischer[1] | Declan Noone[4] | Debra Pollard[5] | Eveline Mauser-Bunschoten[1] | Kate Khair[6] | Keith Gomez[5] | Ellen van Loon[7] | Catherine N. Bagot[8] | Petra Elfvinge[9] | Roseline d'Oiron[10] | Rezan Abdul-Kadir[11] | on behalf of the European Haemophilia Consortium (EHC) and the European Association for Haemophilia and Allied Disorders (EAHAD)

[1] Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands

[2] Irish Centre for Vascular Biology, School of Pharmacy and Biomedical Sciences, RCSI, Dublin and National Coagulation Centre, St. James' Hospital, Dublin, Ireland

[3] European Haemophilia Consortium, Brussels, Belgium

[4] President, European Haemophilia Consortium, Brussels, Belgium

[5] Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK

[6] Director of Research, Haemnet, London, UK

[7] Department of Psychology, UZ Leuven, Leuven, Belgium

[8] Department of Haematology, Glasgow Royal Infirmary, Glasgow, UK

[9] Department of Haematology, Karolinska University, Stockholm, Sweden

[10] Centre de Référence de l'Hémophilie et des Maladies Hémorragiques Constitutionnelles, APHP Paris Saclay - Hôpital Bicêtre and Inserm, U 1176 Le Kremlin Bicêtre, France

[11] Department of Obstetrics and Gynaecology, Royal Free London NHS Foundation Trust and Institute for Women's Health, University College London, London, UK

Correspondence
Karin van Galen, Heidelberglaan 100, 3584 CX Utrecht, Postal address: P.O. Box 85500, 3508 GA Utrecht, The Netherlands.
Email: k.p.m.vangalen@umcutrecht.nl

Abstract

Introduction: Despite increasing awareness of issues faced by women and girls with inherited BDs (WGBD), standards of care are lacking, with disparities in diagnosis and treatment for WGBD across Europe. We aimed to develop practical principles of care (PoC) to promote standardization of care for WGBD within European Haemophilia Treatment and Comprehensive Care Centres (HTC/CCCs).

Methods: The co-creation process, supported by the European Association for Haemophilia and Allied Disorders, consisted of four multidisciplinary meetings with health care providers (HCPs) experienced in WGBD care, and European Haemophilia Consortium representatives, combined with broad patient and HCP consultations in the European haemophilia community. Relevant medical societies outside Europe were contacted for confirmation.

Results: We developed ten PoC for WGBD, stressing the importance and benefits of a centralized, multidisciplinary, comprehensive, family-centred approach to support and manage WGBD during all life stages. These PoC emphasise the right to equitable access and quality of care for all people with BDs, irrespective of gender. Multiple medical societies outside Europe also confirmed their support for endorsement.

Conclusions: Ten PoC for WGBD evolved from an iterative process among stakeholders, supported by relevant medical societies worldwide. These PoC can serve as a benchmark for diagnosis and comprehensive multidisciplinary management of WGBD, and improve awareness of their unique challenges. They offer a framework to guide HTC/CCCs in providing equitable care for all WGBD, both in their own services and in other healthcare settings. Implementation of these principles aims to positively impact the health, wellbeing and quality of life for WGBD.

KEYWORDS

bleeding disorder, heavy menstrual bleeding, postpartum haemorrhage and reproduction, pregnancy, principles of care, women

1 | INTRODUCTION

Provision of care to people with bleeding disorders (BDs) has evolved, from a focus on males with haemophilia to include a broad spectrum of conditions, including von Willebrand disease (VWD), rare factor deficiencies, platelet disorders and other rare bleeding disorders. This implies that growing numbers of women and girls are diagnosed with and treated for BDs (WGBD). Evolution of care is challenging to respond to for both patients and Haemophilia Treatment/Comprehensive Care Centres (HTC/CCCs). Many of the unique challenges that WGBD encounter are not currently met by all HTC/CCCs.

Approximately one in five women who presents to a gynaecologist with heavy menstrual bleeding (HMB) have an underlying BD.[1,2] Yet, BD under-diagnosis remains very common with median diagnostic delays of 8–16 years in women and girls.[3–6] Identification of haemophilia carriers (HCs) is inadequate, with genetic testing often delayed (median age 30 years), and 31% of women being unaware of their carrier status at time of delivery, despite a known family history.[7,8] In contrast, from HCs who were included in a database, maternal carrier status was established in 94% of pregnancies before conception, which underscores the importance of WGBD recognition and registration.[9]

WGBD remain under-treated, with current approaches to peripartum management failing to reduce post-partum haemorrhage (PPH) risks. Despite the availability of specialist care in HTC/CCCs, over 70% of pregnant HCs did not have HTC contact prior to delivery.[9–13] HCs report more spontaneous bleeding and are at higher risk of prolonged bleeding post-surgery, tooth extractions and tonsillectomy, all suggesting inadequate preventive measures.[14,15] HMB is a major issue, consistently reported by WGBD across different inherited BDs, interfering with normal life. Better management is required, clearly evidenced by WGBDs' experiences.[16–18]

Next to physical health, BD may negatively influence social activities and sexual relationships. BD diagnosis may severely impact WGBDs' decisions to have children.[16] These women face increased risks of psychological health issues due to symptoms and/or the potential risks to their children.[19] Open discussion of HMB with health care professionals (HCPs) and even close family members is hampered by menstruation stigma.[4] Proactive HCP engagement, including addressing associated psychosocial issues, is necessary to better manage WGBD.[17,20,21]

This multidisciplinary co-creation project seeks to define European Principles of Care (PoC) for the management of WGBD, which can serve as a benchmark for diagnosis and provision of comprehensive multidisciplinary care, to support HTC/CCCs in providing equitable care for WGBD in their own services and other healthcare settings.

2 | METHODS

These PoC are a joint initiative of the multidisciplinary Women and BDs Working Group of the European Association for Haemophilia and Allied Disorders (EAHAD) and the European Haemophilia Consortium (EHC). The co-creation process consisted of four multidisciplinary meetings with European WGBD experienced HCPs and EHC patient representative, and consultations with the broader European haemophilia patient- and HCP community (Figure 1). The PoC were designed to complement and enhance current HTC/CCC clinical practice and seek to guide optimal quality of care for WGBD, including patient involvement. The statements and statement texts were aimed to be timeless, as inclusive as possible and provide clear advices to support clinical practice in HTC/CCCs across the world.

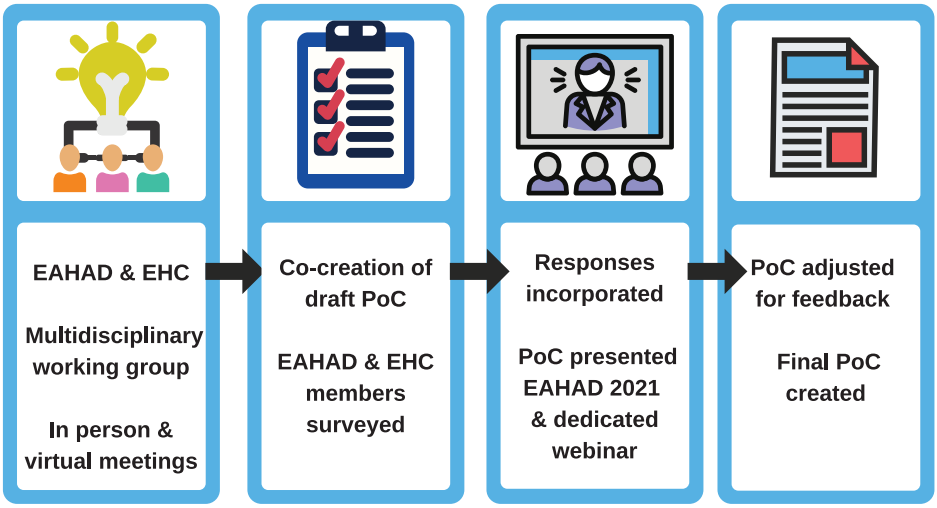


FIGURE 1 Principles of care for women and girls with bleeding disorders co-creation flowchart. Abbreviations: PoC, principles of care; EAHAD, European Association for Haemophilia and Allied Disorders; EHC, European Haemophilia Consortium; EAHAD 2021, the virtual annual EAHAD conference in 2021

The European multidisciplinary team consisted of 6 haematologists, 1 paediatric haematologist, 3 haemophilia nurses, 1 research director, 1 obstetrician gynaecologist, 1 patient/patient representative and 1 psychologist. Following the development of draft statements, feedback was sought from the full EAHAD community and 10–15 EHC WGBD. These stakeholders were consulted via online survey, querying completeness/feedback on each statement. PoC amendments were made based on 51 responses, including 5 from WGBD. These data are available on request from EAHAD with permission of the corresponding author. In addition, the PoC were reviewed by the EHC prior to completion. After completion, the following international societies were asked for their review and support: the Foundation for Women and Girls with Blood Disorders (USA), National Hemophilia Foundation (USA), International Society on Thrombosis and Haemostasis Scientific and Standardization Committee on Women's Health Issues in Thrombosis and Haemostasis, the World Federation of Hemophilia (WFH) Women Inherited Bleeding Disorders Committee (WIBD) and WFH Medical Advisory Board. Furthermore, the PoC were presented at the virtual EAHAD 2021 conference as e-poster and afterwards, on March 9th 2021, a Webinar was organized for discussion, open to both patients and HCPs (> 80 participants), after which final amendments to the PoC paper were made.

TABLE 1 10 European principles of care for women and girls with inherited bleeding disorders

1. Equitable access and quality of care for all individuals with bleeding disorders, irrespective of gender
2. Timely and accurate diagnosis of bleeding disorders in women and girls
3. Awareness of the additional challenges faced by WGBD throughout life
4. Provision of comprehensive care in a family centred approach
5. Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team
6. Education of WGBD and their families regarding the menstrual cycle and its management
7. Early recognition and optimal management of heavy menstrual bleeding
8. Provision of pre-conception counselling and access to prenatal diagnostics
9. Provision of a patient-centred comprehensive management plan throughout pregnancy and the post-partum period
10. Involvement of WGBD in registries, clinical research and innovation

3 | RESULTS

The 10 European PoC for WGBD are stated in Table 1 and explained below. A infographic is provided (Figure 2). All 2.

3.1 | PoC 1 equitable access and quality of care for all individuals with BDs, irrespective of gender

To use the term 'haemophilia' in the centre name may detract attention from other BDs, which occur more frequently and may impact more severely on women and girls. Management of WGBD currently lacks standardization. A survey among 59 European HTCs showed that 58% do not offer combined gynaecology/haematology clinics and 42% lack HMB management strategies.[22] The absence of expertise and defined algorithms for WGBD care perpetuates disparities. WGBD require access to care for both female-specific and general bleeding symptoms.

Ensuring equitable and improved HTC access requires general HCP training to emphasise that BDs are not limited to males or haemophilia, and education on bleeding symptoms, particularly female-specific bleeding, to improve recognition and earlier referral. Once diagnosed, HTC/CCCs should provide access to appropriate multidisciplinary care, treatments and counselling.

TABLE 2 Summary of suggested actions towards implementation for each principle of care

PoC	Implementation actions
1. Equitable access and quality of care for all individuals with bleeding disorders, irrespective of gender	• Ensure access to care for both female-specific and general bleeding symptoms • Appropriate multidisciplinary care, treatments and counselling
2. Timely and accurate diagnosis of bleeding disorders in women and girls	Expedite referral • Education of public and HCP of normal and abnormal bleeding patterns ○ Focus on Paediatricians, GPs, Gynaecologists, ENT, dentists, POs • Clear referral pathways and criteria Assessment • Expert haematology involvement in haemostasis testing and interpretation • Use of standardised BAT to determine phenotype HTCs • Systematic approach to identification and testing of female carriers • Registration of WGBD, with appropriate registration of HCs
3. Awareness of the additional challenges faced by WGBD throughout life	• Education – WGBD and HCPs • Psychological support for bleeding symptoms ○ Optimise QoL, work/school and sports participation, sexual and reproductive functioning • Improved medical management ○ WGBD empowerment ○ More effective self-management ○ Individual treatment plans ○ Avoidance of unnecessary surgical interventions
4. Provision of comprehensive care in a family centred approach	• Every patient contact is an opportunity to identify other affected family members/carriers • Provide family centred approach to education • Smooth transition of care - adolescents to adult services
5. Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team	• Better communication – among HCPs and with WGBD • Multidisciplinary management plans, clinical guidelines • Individualized patient-centred care plans
6. Education of WGBD and their families regarding the menstrual cycle and management	• Medical societies and POs supported education programs adopted locally by HTC/CCC • Age-appropriate and culturally sensitive written information • Assist in self-assessment and -management • Planned strategies on prevention and immediate access to care for abnormal bleeding
7. Early recognition and optimal management of heavy menstrual bleeding	• Awareness of increased risk HMB at menarche and peri-menopause • Regular and standardized assessment of menstrual blood loss (PBAC) and iron levels • Clear pathways for diagnosis and treatment of HMB providing personalized treatment
8. Provision of pre-conception counselling and access to prenatal diagnostics	• Comprehensive, timely preconception counselling (checklists) • Prenatal diagnostics options available and safety discussed (pathways)
9. Provision of a patient-centred comprehensive management plan throughout pregnancy and the post-partum period	• Clear birth plans and management protocols • Patient and partner involvement • Assessment of clotting factor status and iron levels • Awareness/anticipation/education on both primary and secondary PPH • Anticipate neonatal bleeding risks
10. Involvement of WGBD in registries, clinical research and innovation	• Uniform internationally-defined outcome measures • Capturing of WGBD and female-specific outcome measures in databases • Sex-specific pharmacovigilance and drug development • Active involvement of WGBD in study aim & design

Abbreviations: BAT, bleeding assessment tool; ENT, ear nose throat; GP, general practitioner; HC, haemophilia carrier; HCP, health care provider; HMB, heavy menstrual bleeding; HTC/CCC, haemophilia treatment/comprehensive care center; PBAC, pictorial bleeding assessment chart; PO, patient organization; PoC, principles of care; PPH, post-partum hemorrhage; QoL, quality of life; WGBD, women and girls with bleeding disorders.

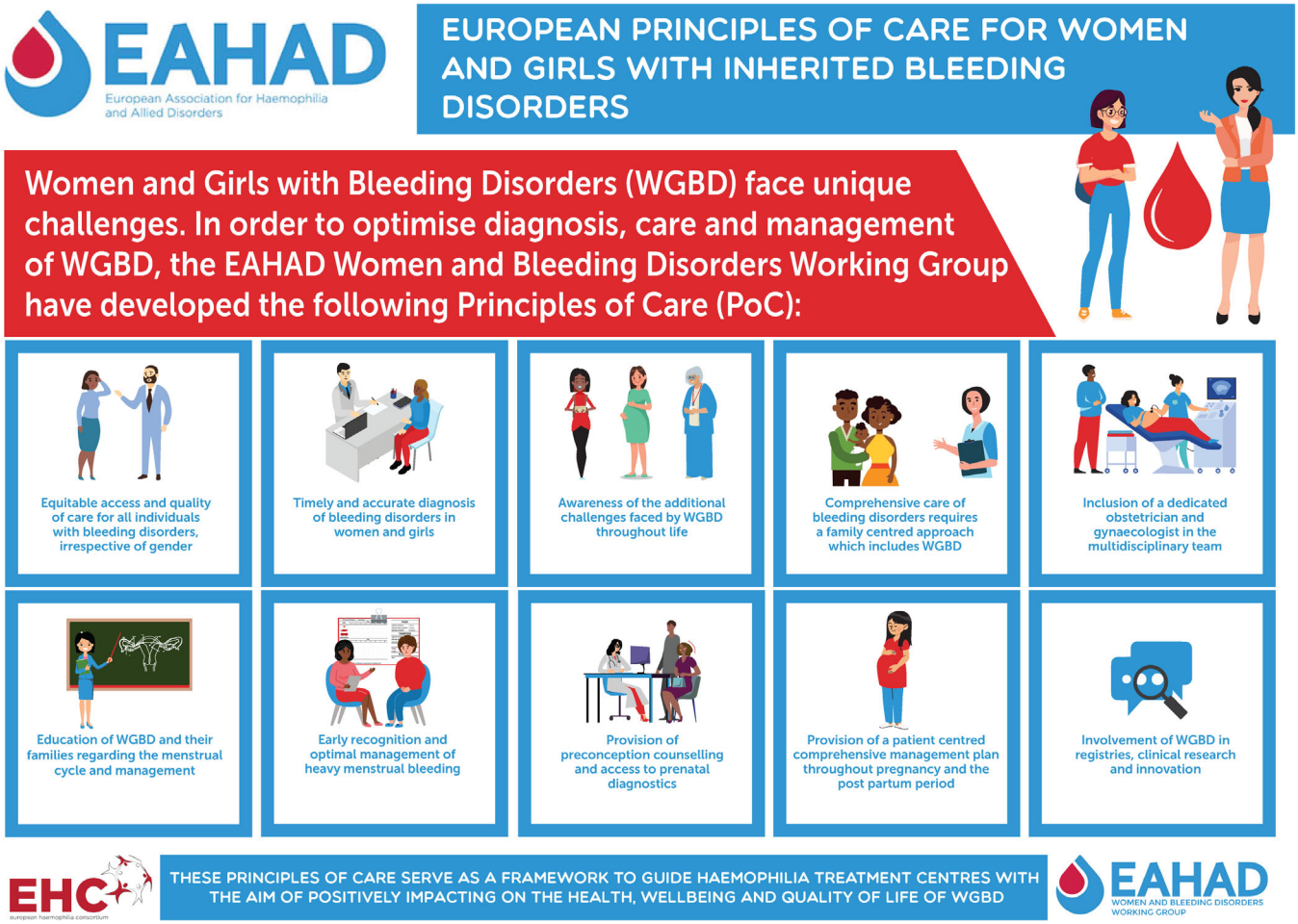


FIGURE 2 Infographic outlining the ten Principles of Care for Women and Girls with Bleeding Disorders

3.2 | PoC 2 timely and accurate diagnosis of BDs in women and girls

Significant diagnostic delays, which occur in most BDs, hamper accurate management especially for WGBD.[3,6,23] HMB can be the sentinel symptom of a BD, particularly in adolescents.[24] Barriers to early diagnosis relate to inadequate recognition of symptoms, lack of systematic family inquiry, normalisation of bleeding symptoms within BD families, and insufficient awareness amongst HCPs regarding the impact of BDs.[16,18,25]

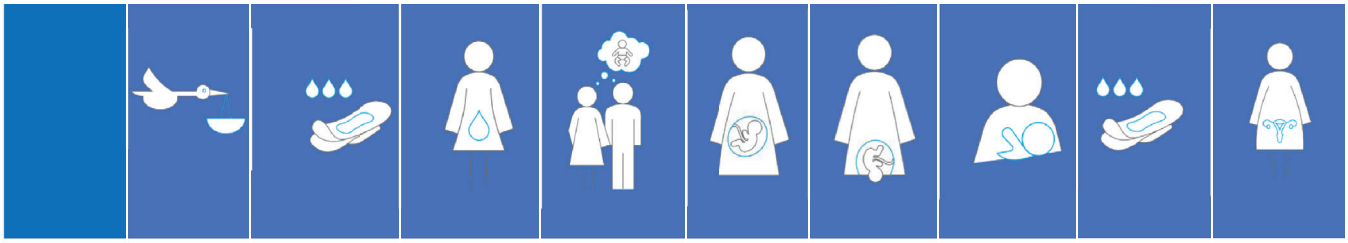
While bleeding symptoms occur frequently, identification of HCs is often delayed, even beyond pregnancy with potential adverse neonatal outcomes.[7,8,14,15] HCs with Factor VIII or IX levels < 0.40 IU/mL should be registered and managed as having haemophilia. Bleeding may also occur in HCs with FVIII/FIX levels of ≥0.40 IU/mL, which is associated with lower quality of life (QoL).[14,15,26–28] A newly proposed HC nomenclature acknowledges 'symptomatic HC' as a separate category of HCs with a bleeding phenotype, next to women and girls with mild, moderate or severe haemophilia.[29]

Active testing and regular family-history updates are key to promote appropriate diagnosis and referral. In BD families, assessment of relevant clotting factor and bleeding phenotype should be performed during early childhood, along with family education (PoC 3&4) and repeated before menarche (PoC 6&8). If a causative mutation is identified, all potential affected individuals/carriers should be offered genetic counselling, and tested when competent to understand the implications, generally in early adulthood. Genetic testing in childhood can also be considered when clinically relevant (PoC 8).[30]

General awareness and knowledge on WGBD should be increased in patients and HCPs, including paediatricians, general practitioners, dentists and gynaecologists. Collaborative engagement of both patient organizations and HTC/CCCs is required to educate the public and medical communities regarding: abnormal bleeding symptoms (PoC 7); inheritance (PoC 8); bleeding risk assessment; appropriate laboratory testing; and HTC referral criteria. Defined diagnostic pathways and (self-)bleeding assessment tools can reduce delays.[31,32]

3.3 | PoC 3 awareness of the additional challenges faced by WGBD throughout life

WGBD may experience general bleeding symptoms, such as epistaxis, dental bleeding, joint bleeding and post-operative bleeding, but also face additional female-specific challenges (Figure 3). Excessive and/or



Life stage	Infancy/ childhood	Adolescence	Young adulthood	(Pre) Conception	Pregnancy	Delivery	Breast feeding	Mid/late adulthood	Menopause
Education needs	Testing for clotting factor levels Bleeding symptoms Introduce MDT	Normal menstrual cycle Sexual education ID(A) symptoms Genetic testing	PBAC HMB Ovulation bleeding Hormonal suppression Inheritance	Genetic counselling Choices including PGD Current treatment perspectives	PND MD delivery plan	PPH Primary Secondary ID(A) symptoms	Safe use of TXA Contracep-tion / hormonal suppression	PBAC HMB Treatment options depending on fertility choices	Hormonal suppression Gynae input

FIGURE 3 Educational needs on additional challenges of WGBD. Abbreviations: WGBD, woman and girls with inherited bleeding disorders; HMB, heavy menstrual bleeding; PBAC, pictorial bleeding assessment chart; PND, prenatal diagnostics; PGD, pre-implantation genetic diagnosis; MD(T), multidisciplinary (team); ID(A), iron deficiency (anaemia); PPH, post-partum haemorrhage; TXA, tranexamic acid; Gynae, gynaecologist

prolonged bleeding can occur during menstruation, especially around menarche, peri-menopause, during ovulation, miscarriage, pregnancy termination and childbirth. HMB is most frequently encountered (PoC 7).[16]

Patients and HCPs may not always be aware of the rates and severity of HMB, which may cause morbidity or even mortality if left untreated.[33] Haemorrhage during ovulation, although infrequent, should prompt consideration of an underlying BD. Without early recognition, the resultant haematoperitoneum may require emergency surgery and even oophorectomy, compromising fertility.[34] The hereditary nature of coagulopathies poses additional challenges in reproductive decision-making and delivery management (PoC 8 & 9).

WGBD should be managed in a HTC where education of both HCPs and patients are essential to prevent and treat female-specific bleeding complications. A treatment plan, including emergency room card, common for males with haemophilia, is the first step to improve quality of care for WGBD. This should be updated throughout life and include management of female specific bleeding (PoC 7 & 9).

HCPs should be aware that bleeding symptoms, including stigmatizing hematomas, may have specific physical and psychological implications. HMB is associated with pain, tiredness, poor QoL, work/school absence at significant economic costs, reduced sports participation, and impacts on sexual and reproductive functioning.[16,35] Misdiagnosis and under-treatment may lead to undesired medical events, such as hysterectomy at a young age complicated by post-operative bleeding.[20] Improved recognition and treatment, as well as addressing psychosocial issues in a multidisciplinary manner, can avoid unnecessary costly procedures and social impairment.[36,37] Good education of HCPs, WGBD and families raises awareness, enables improved personalized care and effective self-management (Figure 2, Table 2).

3.4 | PoC 4 provision of comprehensive care in a family centred approach

BDs affect whole families, not just individuals, due to inheritance, impact of a patients' bleeding symptoms on family members, social impact, loss of productivity, stress, anxiety and other concerns related to bleeding episodes.[38–41] HMB represents a monthly bleeding challenge and, even in the general population, impacts normal daily life in up to one third of women. Menstruation is not openly discussed within families and normalization of HMB within affected families adds to the undisclosed burden of disease.[17,42,43] Encouraging a shift in perspective in HTCs from individual patient- towards family care and education is required to address these issues.

When an inherited BD is diagnosed or suspected in a girl, both parents should be educated on female-specific bleeding symptoms (PoC 3, Figure 2). HMB management advice at menarche supports parents in preparing, and facilitates communication about gynaecological bleeding (PoC 6). In transition programmes, family-focused care should be balanced with increasing adolescents' individual

responsibility to establish a new foundation of trust for both patient and parents towards adult care.[44]

For every man with haemophilia 2.5-5 potential and 1.6 actual HCs can be identified among female relatives.[45] A narrow focus on males with haemophilia leads to missed diagnoses of symptomatic carriers and women/girls with haemophilia, risking iatrogenic bleeding and impaired joint health.[8,45,46] Besides haemophilia, all families with inherited BDs should be offered easy HTC access. Every patient contact provides an opportunity to identify affected family members (PoC 2), and provide access to haemostatic testing, comprehensive care and genetic counselling for family members.[47]

In addition to a family centred patient management approach, affected families should be educated about inheritance, reproductive options and barriers to family disclosure.[48,49] Genetic counselling must recognize the central role family experiences play in reproductive choices/experiences.[46,50–53] All WGBD and partners, including possible or established carriers, should be encouraged to attend the HTC/CCC in advance of planning pregnancy to ensure the best possible outcome for mother and child (PoC 8).[45,48]

3.5 | POC 5 inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team

The importance of multidisciplinary HTC management for people with BDs has long been recognized.[54,55] For WGBD, the most common bleeding symptoms during reproductive life relate to menstruation and gynaecological issues. Pregnancy, delivery and the postpartum period are critical times for WGBD requiring special attention.[56] All HTCs should establish and facilitate strong collaboration with their local obstetrics and gynaecology team, including adolescent gynaecology, to improve continuity of care for WGBD and optimize management.

Multidisciplinary care can be delivered via combined or joint clinics, where patients meet all relevant HCPs during one visit, including nurses and social workers if needed, and provide women with individualized patient-centred care plans. Joint clinics, whether delivered face-to-face, as telemedicine or hybrid constructions, benefit interaction between patients and relevant HCPs, improve patients' satisfaction and reduce hospital visits.[55] Formalized inclusion of obstetricians/gynaecologists in the multidisciplinary HTC team also increases BD visibility within this HCP community, improving awareness and facilitating earlier diagnosis.

3.6 | PoC 6 education of WGBD and their families regarding the menstrual cycle and its management

Over a lifetime, women average 450 menstrual cycles, each time facing haemostatic challenges of ovulation and menstruation.[57,58] In order to improve understanding and awareness, HTC/CCCs should provide education and counselling about the menstrual cycle to WGBD and their families.

Consultations should be supported by age-appropriate and culturally sensitive written information. Each WGBD should learn what is normal/acceptable and expected during menarche, ovulation, menstruation and menopause. HTC/CCCs and patient organisations can help improve awareness of unusual symptoms, assist in self-assessment and facilitate early intervention when needed to empower WGBD.

Adolescent girls are at particular risk for HMB due to ovarian immaturity and high rates of anovulatory cycles.[24] To avoid disruptive bleeding during adolescence, prior to menarche, HTC/CCCs should prepare girls and family members for what to expect and when to seek HTC assistance. Designing early management strategies helps to prevent or control HMB/ovulatory bleeding, especially acute episodes and their consequences. HTC/CCCs should meet the needs of girls and their families when planning paediatric to adult services transition (PoC 4). An adolescent gynaecologist could be consulted if needed.

Perimenopause and menopause are critical times, when menstrual bleeding may increase and cycles become irregular. Women should be provided with information in advance on changes in menstrual pattern and menopausal symptoms, and how/when to access specialist medical care if required. If surgical treatment is deemed necessary, assessment and proper management of the individual bleeding risks are essential, to prevent bleeding complications.[20,59]

3.7 | POC 7 early recognition and optimal management of heavy menstrual bleeding

Subjective reporting of menstrual bleeding may be unreliable and affected by cultural and language barriers.[60] Duration, heaviness and frequency of menstrual loss should therefore be recorded using pictorial bleeding assessment charts (PBAC), to improve awareness, quantify blood loss and assess treatment efficacy.[32] Both haemoglobin and iron stores should be assessed regularly and managed as appropriate with early iron replacement therapy.[61,62] Next to these traditional measures, multidisciplinary HTC/CCC care should focus on patients' satisfaction, QoL and reach out to school/work place if needed.

In WGBD, treatment options for HMB include haemostatic agents (such as tranexamic acid, factor replacement therapy), hormonal therapies (such as oral contraceptive agents), or combinations, and rarely surgical options.[63] Consideration of the use of hormonal intrauterine devices (IUDs) is not dependent on age or parity as studies have identified these IUDs as an appropriate and effective treatment option for adolescents with HMB.[64] HTC/CCCs should offer treatment options, personalized according to age, fertility/pregnancy wishes, other gynaecological symptoms, patient's views and acceptance of treatment options and side effects, respecting cultural and psychological aspects.[19]

HMB in WGBD may not always be caused by their coagulation defects, but can be due to structural causes such as polyps, fibroids, endometriosis and endometrial pathologies. Hence close collaboration with gynaecological teams is essential to facilitate timely and appropriate gynaecological investigations and treatments.

3.8 | PoC 8 provision of pre-conception counselling and access to prenatal diagnostics

WGBDs may face difficult choices when planning a family. Counselling should be available that covers the prospective mother's own bleeding risk as well as the inheritance pattern and risks for the offspring. Available options for mitigating these risks should be discussed as soon as WGBD feel ready, preferably repeatedly, and they should feel able to make choices freely without fear of judgment.[21]

For severe BDs, strategies to prevent transmission of the causative variant include pre-implantation diagnosis (PGD) and pre-natal genetic diagnosis (PND).[65] PGD involves in-vitro fertilization with selection of genetically-tested embryos that are negative for the familial causative variant. Sufficient time should be reserved to discuss the burden, risks and benefits of PGD, including any maternal bleeding risk associated with the related invasive procedures. The availability of PGD may be limited for financial, technological, cultural and ethical reasons; WGBD should be informed about limitations and any criteria used to enable access to this option.[66]

Counselling regarding natural conception should focus on the probability of an affected or carrier child and what clinical phenotype to expect. Clear HTC pathways should ensure that PND is available promptly if the mother wishes to consider termination of pregnancy in case of an affected child. This comprises non-invasive options (in case of haemophilia, foetal sex determination by ultrasound or analysis of free foetal DNA in maternal plasma) and invasive procedures (chorionic villus sampling or amniocentesis). Parents-to-be should be aware that invasive PND procedures carry a slight additional risk of miscarriage.[67,68] In the future, free foetal DNA may be sufficiently sensitive to determine the foetus' exact genetic status obliviating the need for invasive tests.[69,70]

Late PND to guide obstetric management should be offered in pregnancies of foetuses with a high risk of neonatal bleeding during delivery. This requires amniocentesis in the mid third trimester, and the mother should be counselled regarding the small risk of premature delivery.[71]

3.9 | PoC 9 provision of a patient-centred comprehensive management plan throughout pregnancy and the post-partum period

WGBD are at a higher risk of both primary and secondary PPH, and their new-borns, who may inherit the BD, are at risk of bleeding during birth, particularly with instrumental delivery.[10,12,72,73] Next to obvious physical and medical consequences, PPH has potential negative impact on mental health. A negative birth experience may increase anxiety influencing future pregnancies and deliveries.[74–76]

Iron levels should be checked, and iron deficiency treated during pregnancy to mitigate the risk of adverse maternal and neonatal outcomes.[62] To enhance a sense of safety and autonomy during childbirth, the parents-to-be should be involved in preparing the birth plan.[21] This includes a discussion about where the birth will take place: at a regional centre with expertise (HTC) or local nearby hospital. Clear communication, documentation, provision of the birth plan to the future parents, and all relevant HCPs expected to be involved in care, is essential to ensure a safe delivery. Prior to discharge after delivery, women should be informed regarding normal lochia and the signs of late PPH, and be aware of how, when and where to seek medical attention.

HTCs should draft a clear multidisciplinary birth plan, with an interim plan in place from 24 weeks to cover all eventualities, including preterm delivery, to be adjusted at 28–36 weeks based on reassessment of clotting status and PND results. It includes clear and specific advice regarding haemostatic management during delivery and postpartum, suitability for neuraxial anaesthesia, foetal restrictions requirements for safe delivery (if any) and postpartum neonatal management.[45,77–79] Cord blood testing may be needed and referral for haemostasis testing of possibly-affected children to a paediatric haematologist. Next to specific haemostatic treatments, tranexamic acid reduces the risk of early and late PPH, does not impede breastfeeding.[73,80–82] Its immediate, as well as prolonged use after delivery should therefore be considered for all women with increased bleeding tendencies.

3.10 | PoC 10 involvement of WGBD in registries, clinical research and innovation

Data on WBGD is limited. Standardized inclusion of WGBD in (inter-)national registries is lacking and clinical research on impact and management of BDs remains focused mainly on males with haemophilia.[83] To improve our knowledge of WGBD, consistent and harmonized inclusion of WGBD in national/international BD registries is required. Uniform, internationally-defined patient relevant (female-specific) outcome measures should be used to enable better understanding of the impact of BD in women and which treatments effectively reduce female-specific bleeding and its consequences.

It is insufficiently acknowledged that sex-based differences impact pharmacokinetics, hampering therapeutic optimization.[83] Increased attention should be paid to sex-specific pharmacovigilance and drug development.

To ensure best WGBD treatment and outcome assessment this patient group should be involved in clinical research as well as study conception, co-design and scientific boards. Study protocols should capture women-specific outcome measures. Only then medical innovation will truly be aimed at improving QoL for WGBD.

3.11 | Limitations and challenges

Different healthcare systems will have varying constraints on the resources available for change implementation. As such, the challenges associated with introduction of these PoC will vary internationally and even within countries depending on the local services. We encourage each HTC/CCC to examine the feasibility of implementation of PoC

and to prioritise according to the currently available resources and the areas of greatest need for development. An important first step for each HTC/CCC is to establish a close relationship with an associated gynaecology/obstetric service, which will hasten improvements in the other PoCs. With the increased availability of telehealth consultation this option should also be explored to facilitate interactions with patients in a potentially time and cost effective manner, particularly in remote locations.

4 | CONCLUSIONS

Ten PoC for WGBD have been defined based on an iterative process within the European BD community. These PoC can serve as a benchmark to improve awareness of unique WGBD challenges and support their diagnosis and comprehensive multidisciplinary management. They offer a framework for HTC/CCCs to provide equitable care for all WGBD, both in their own services and other healthcare settings. PoC implementation and adherence is expected to positively impact WGBD's QoL, improve their social participation and engagement in clinical care and research. Potential limitations and challenges regarding implementation of these PoC remain to be evaluated, as well as its impact on future WGBD experiences, to ensure adequate uptake and representation with regard to race, ethnicity, culture, and social determinants of health factors.

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CONFLICT OF INTEREST

Dr. van Galen has received unrestricted research grants from CSL Behring and Bayer and Octapharma and speakers fee from Takeda, CSL Behring and Bayer. Dr. Lavin received consultancy fees for Takeda and an advisory board for Tremeau Pharmaceuticals, and served as a consultant for Sobi. D. Pollard received speakers fee from CSL, Roche-Chugai, NovoNordisk, Sobi, Takeda and advisor/consultancy fees from BioMarin, CSL, Takeda, Roche, NovoNordisk. Dr. d'Oiron has served as a consultant for Baxalta/Shire, Bayer, Biomarin, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche and Sobi, Spark and was invited speaker for Baxalta/Shire, Bayer, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche and Sobi. Dr Khair has received unrestricted research grants from CSL Behring, Pfizer, Roche, SOBI, uniQure and consultancy/speaker fees from Bayer, Biomarin, CSL Behring, HCD Economics, Novo Nordisk, Pfizer Roche, SOBI and Takeda. Dr. Fischer has received speaker's fees from Bayer, Baxter/Shire, SOBI/Biogen, CSL Behring, NovoNordisk; performed consultancy for Bayer, Biogen, CSL-Behring, Freeline, NovoNordisk, Roche and SOBI; and has received research support from Bayer, Baxter/Shire, Novo Nordisk, Pfizer and Biogen. Dr Gomez has received unrestricted research grants from Bayer and Pfizer and, consultancy and speaker fees from Bayer, Biomarin, BPL, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, Sobi and Takeda. Prof Abdul-Kadir received lecture fees/ educational grants from Pfizer, NovoNordisk, Takeda and ViforParma.

None of the other authors has any conflicts of interest to declare.

ORCID

Karin van Galen https://orcid.org/0000-0003-3251-8595
Michelle Lavin https://orcid.org/0000-0003-2999-4216
Kathelijn Fischer https://orcid.org/0000-0001-7126-6613
Kate Khair https://orcid.org/0000-0003-2001-5958
Keith Gomez https://orcid.org/0000-0002-8934-0700
Roseline d'Oiron https://orcid.org/0000-0002-4843-7805
Rezan Abdul-Kadir https://orcid.org/0000-0002-2684-1006

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