



EMLc

ATC codes: B05AA02

Indication	Coagulation defects, purpura or other haemorrhagic or related conditions ICD11 code: 3B6Z
Medicine type	Biological agent
List type	Core (EML) (EMLc)
Formulations	Injection: frozen liquid in bag or lyophilized powder in vial containing: > 50 IU Factor VIII > 100 IU vWF > 140 mg clottable fibrinogen per unit
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	cryoprecipitate (not pathogen-reduced) (ATC codes: B05AA02)
Patent information	Patents have expired in most jurisdictions Read more about patents .

Tags

Biological

Wikipedia

[Cryoprecipitate \(pathogen-reduced\)](#)

Expert Committee recommendation

The Expert Committee recognized that insufficient access to clotting factor replacement products contributes to early death in patients with bleeding disorders. Accessibility to these products is especially problematic in low- and middle-income countries where many patients have no access to any form of treatment. The Committee considered that evidence and extensive clinical experience suggest that cryoprecipitate is superior to plasma for replacement of certain clotting factors in a variety of indications in adults and children. However, the Expert Committee noted that concentrated clotting factors remain the preferred treatment for many bleeding disorders and should be prioritized for selection and use wherever possible. The Committee noted and agreed with the WHO Blood Regulatory Network position statement and emphasized that cryoprecipitate-PR ought only to be used in settings where commercial clotting factors are unaffordable or unavailable. The Committee was not in the position to recommend specific methods of pathogen reduction but considered that cryoprecipitate-PR developed using validated, approved pathogen-reduction methods should be ensured. The Committee also noted that comparative evidence for cryoprecipitate-PR versus non-pathogen-reduced cryoprecipitate was limited but acknowledged that pathogen reduction can eliminate major risks of transmission of bloodborne infectious agents and increase the safety of administration. While there is a risk of alloimmunization and allergic transfusion reaction, these adverse events are lower than rates reported for other blood components, including fresh frozen plasma. The Expert Committee therefore recommended the inclusion of cryoprecipitate-PR on the core list of the EML and EMLc for use in the replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and shortage of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate for patients with haemophilia A in settings where this product is unavailable or unaffordable. The Committee also recommended that non-pathogen-reduced cryoprecipitate be included in the Model Lists as a therapeutic alternative given that transition to cryoprecipitate-PR at the country level may take time. The Committee acknowledged that solvent and detergent virus inactivation technologies and medical devices used in the plasma fractionation industry are gaining momentum, and are being adopted by an increasing number of blood

establishments and national blood service centres. The Committee considered that every effort should be made to facilitate the transition to cryoprecipitate-PR, and processing systems should be adopted based on virus inactivation technologies. For this reason, the Committee considered that removal of non-pathogen-reduced cryoprecipitate from the Model Lists as a therapeutic alternative to cryoprecipitate-PR should be considered at the earliest opportunity (i.e. 2025) unless an application is received to support its retention. The Committee emphasized the requirement that all blood, blood components and plasma derivatives used as essential medicines should comply with WHO requirements developed by the WHO Expert Committee on Biological Standardization. The Committee also emphasized that blood donor and donation screening for infections before use of blood products should always be implemented.

Background

Cryoprecipitate-PR has not previously been considered for inclusion on the Model Lists. At its meeting in 1989, the Expert Committee recommended addition of a square box symbol to the listing for coagulation factor VIII, to accommodate cryoprecipitate as a therapeutic alternative (1).

Public health relevance

Fresh frozen plasma is listed on the WHO Model Lists and has been used historically to replace clotting factors in severely bleeding patients. However, it does not contain the deficient clotting factors in concentrated form and when used in severe bleeding, volume overload (transfusion-related acute circulatory overload) due to large volume infusions limits the correction of plasmatic coagulation in the bleeding patient. In particular, in massive bleeding, fibrinogen is low in comparison with other clotting factors necessitating targeted replacement. In contrast, cryoprecipitate-PR and cryoprecipitate contain the following procoagulant plasma proteins in concentrated form: factor VIII (anti-haemophilic factor (AHF)); von Willebrand factor; fibrinogen; and factor XIII. Thus, they can be used for treatment of patients with defined inherited bleeding disorders or acquired bleeding disorders. Incidence and prevalence of inherited and acquired bleeding disorders Haemophilia A has a reported incidence of 1 in 4000 male births (2). The worldwide prevalence is around 200 000 diagnosed patients (3). The actual prevalence may be higher as many people with haemophilia A in low- and middle-income countries are undiagnosed. Almost all patients are males and the incidence of haemophilia is the same regardless of race or ethnicity (4,5). Symptomatic von Willebrand disease has a reported incidence of 1 in 10 000 (2). The prevalence of symptomatic patients with von Willebrand disease is around 90 000 (3). The overall prevalence (including all types and severity forms) is relatively high, with up to 1% of the population being affected (6,7). The incidence is the same in females and males, although women suffer more often from clinical bleeding due to menstruation and child delivery. Afibrinogenemia, dysfibrinogenemia and factor XIII deficiency each have reported incidence of 1 in 1 million and the prevalence is very low (8). The incidence of acquired hypofibrinogenemia and acquired factor XIII deficiency due to peripartum haemorrhage correlates with the level of care and surveillance during pregnancy and with gynaeco-obstetric services at child delivery. The magnitude of the disease can be derived from data on maternal mortality, which is largely due to intra- and postpartum massive haemorrhage. According to WHO, about 287 000 women died during and following pregnancy and childbirth in 2020. The maternal mortality ratio in low-income countries in 2020 was 430 per 100 000 live births. WHO data indicate that the vast majority of deaths occurred in low- and middle-income countries, ranging from 30 to 1223 per 100 000 live births in nine countries considered as so-called fragile states (9). Postpartum haemorrhage is the main cause of maternal mortality and morbidity across the world, responsible for more than 25% of such deaths annually. WHO statistics suggest that 60% of maternal deaths in developing countries were due to postpartum haemorrhage, accounting for more than 100 000 maternal deaths a year worldwide. The frequency of massive bleeding and resulting clotting disorders due to (poly)trauma (often related to traffic crashes or work accidents) is also correlated with, for example, the human development index, gross domestic product and performance of national/local health care systems. Developing economies record higher rates of road traffic injuries, with 93% of fatalities from low- and middle-income countries (10). Use of specific coagulation factor concentrates is preferred to the use of cryoprecipitate-PR and cryoprecipitate in these conditions. However, supplies of coagulation factor concentrates (plasma-derived or recombinant) are insufficient in low-income countries and are limited relative to demand in lower middle-income countries mainly because of their high costs. Where coagulation factor concentrates are available in low-income settings, they are generally products donated by industry and distributed mainly by charitable organizations or through the World Federation of Hemophilia Humanitarian Aid Program.

Benefits

Similar to other blood components that have been in widespread use before the era of rigorous controlled trials, effectiveness of cryoprecipitate was never formally demonstrated. Nevertheless, clinical experience over more than 50 years has established the superiority of cryoprecipitate to plasma for replacement of certain clotting factors (factors I, VIII and XIII, and von Willebrand factor) based on its ability to deliver these plasma proteins with a low-volume of product. Comparative effectiveness data of cryoprecipitate-PR versus cryoprecipitate are limited. The application described different types of cryoprecipitate-PR available and used in different countries. Cryoprecipitate-PR made with VIPS solvent detergent virus inactivation kits (VIPS S/D), is prepared from pools of about 30–35 units of conventional low-volume (i.e. highly depleted of cryoprecipitate-poor plasma called “dry”) cryoprecipitate that are treated by solvent detergent and bacterial filtrations to inactivate and remove pathogens. Consistency of the content of active factor VIII, von Willebrand factor, clottable fibrinogen and factor XIII has been demonstrated (11). Human trials in Egypt included pharmacokinetics of factor VIII, a safety and efficacy study in therapeutic plasma exchange, and a small observational study in children with severe haemophilia A who received prophylactic therapy with VIPS S/D cryoprecipitate for 2–5 years. Additional safety and efficacy data were reported based on clinical use in more than 2000 patients. The study results and additional clinical reports demonstrated and confirmed that the pharmacokinetics, safety and efficacy of cryoprecipitate factor VIII derived from solvent detergent virus inactivation kits is similar to plasma-derived and recombinant factor VIII concentrates prepared by large-scale plasma fractionation, and possibly also has a reduced risk of factor VIII inhibitor development (12). Heat-treated freeze-dried cryoprecipitate made from small pools of plasma has been used for factor VIII replacement in Thailand since 1997 (13). Factor VIII concentrate is now manufactured by plasma fractionation locally in Thailand; however, heat-treated freeze-dried cryoprecipitate is still produced to further cover the needs of patients with von Willebrand disease, and fibrinogen or factor XIII deficiency (14). Cryoprecipitate (methylene-blue treated and removed and leukocyte depleted) is described as a source of concentrated factor VIII:C, von Willebrand factor, fibrinogen, factor XIII and fibronectin for use in neonates in the guidelines of the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee for the blood transfusion service (15). In 2021, the United States Food and Drug Administration approved pathogen-reduced cryoprecipitated fibrinogen complex made with the INTERCEPT Blood System for Cryoprecipitation® for: treatment and control of bleeding including massive haemorrhage associated with fibrinogen deficiency; control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor are not available; second-line therapy for von Willebrand disease; and control of uraemic bleeding after other treatment methods have failed. It is not recommended for use for replacement of factor VIII (16). This cryoprecipitate is produced from plasma processed in the INTERCEPT system to inactivate pathogens using exposure to a specific psoralen compound (amotosalen) and irradiation with ultraviolet A light followed by adsorption of residual amotosalen. Cryoprecipitate was used for decades before the development of industrially manufactured concentrates of coagulation factor VIII. Use of cryoprecipitate, preferably pathogen-reduced, is recommended in recognized national and international guidelines when factor VIII clotting factor concentrates are not available. Comparable effectiveness of cryoprecipitate and cryoprecipitate-PR compared with coagulation factor VIII to replace factor VIII in acute treatment of bleeding in haemophilia A results from the fact that infusions of cryoprecipitate and cryoprecipitate-PR can provide equivalent levels of factor VIII compared with clotting factor concentrates, albeit at larger administered volumes. Prophylactic therapy to prevent bleeding is considered the standard of treatment in haemophilia A and home infusion is encouraged to decrease the logistic burden on patients and their families. While useful in acute treatment of bleeding, cryoprecipitate and cryoprecipitate-PR cannot readily be used for prophylactic therapy nor used easily at home.

Harms

Cryoprecipitate has been in clinical use for more than 60 years with very few reports of adverse events. Inherent risks are those of plasma, which include transmission of viruses and bacteria, and allergic transfusion reactions. Compared with plasma, the risks of haemolytic transfusion reactions and volume overload with cryoprecipitate are lower because of the smaller volumes administered. Thrombosis is known to be associated with large volume transfusion therapies with plasma and cryoprecipitate. However, a causal relationship, presumably due to elevated levels of fibrinogen, is not clear (17). The risks of cryoprecipitate-PR include those of cryoprecipitate with added potential risks related to the method of pathogen reduction used in preparation of the specific product. Publicly available data are limited on specific cryoprecipitate-PR products, however safety reporting on two products in current use has indicated no significant added concerns. Pathogen-reduced cryoprecipitated fibrinogen complex made with the INTERCEPT Blood System for Cryoprecipitation® is prepared from INTERCEPT processed plasma. The package insert notes a 15-year history of safe use of INTERCEPT-processed plasma in the European Union for treatment of congenital coagulopathy including fibrinogen

deficiency, acquired coagulopathy including liver transplant, and for therapeutic plasma exchange, where there were no safety signals indicative of excess treatment-related morbidity (16). Safety experience is also reported for VIP S/D cryoprecipitate. Locally prepared VIP S/D cryoprecipitate in Egypt has been used since 2013 for treatment of more than 2000 patients with haemophilia A who received 32 million units of coagulation factor VIII. Extensive preclinical studies predicted a low risk of hazards. Clinical studies by the manufacturer and observational clinical studies at one large centre in Egypt revealed no acute or chronic toxicities. Longitudinal studies included 12 children with haemophilia A who received prophylaxis with a mean annual dose of factor VIII of 1029 IU/kg (range 545–1684 IU/kg) for 2–5 years (internal unpublished data from Shabrawishi Hospital Blood Transfusion Centre in Egypt). Additionally, 32 patients received large volume plasma exchanges with VIP S/D plasma. Four of the 32 patients showed mild adverse events similar to those seen when transfusing normal plasma (18). No signs of acute toxicity due to the solvent and detergent used to reduce pathogens were seen in this product (18). Postmarketing clinical data after 5 years of placement on the market of the first VIP S/D device did not show any demonstrable adverse events whether immediate or delayed. Together, the studies showed that VIP S/D plasma and cryoprecipitate have similar degrees of safety and efficacy compared with factor VIII clotting factor concentrates.

Additional evidence

The following evidence for the effectiveness of cryoprecipitate was identified during the expert review process of the application. A randomized study in Brazil evaluated the haemostatic effects of fibrinogen concentrate compared with cryoprecipitate in 63 children following cardiac surgery with cardiopulmonary bypass (19). No significant difference was seen between treatment groups in the primary outcome of 48-hour postoperative blood loss (median 320 mL, interquartile range (IQR) 157 to 750 mL in the fibrinogen concentrate group (n = 30) versus 410 mL, IQR 215 to 510 mL in the cryoprecipitate group (n = 33); P = 0.672). The post-treatment incidence of allogenic blood transfusion was also similar between treatment groups.

Cost / cost effectiveness

Cryoprecipitate and cryoprecipitate-PR may be less costly to provide than clotting factor concentrates. While this may enable their cost-effective use in resource-constrained settings, cryoprecipitate and cryoprecipitate-PR should not be preferred to clotting factor concentrates. Therefore, facilitation of their preparation and use should not divert national efforts to assure availability of clotting factor concentrates. The relative cost of non-pathogen-reduced cryoprecipitate versus clotting factor concentrates has been examined in comparative efficacy studies. For example, in studies comparing cryoprecipitate with commercial concentrates of fibrinogen, fibrinogen concentrates cost two-to-four times that of cryoprecipitate per gram of fibrinogen (24,25). Data on the comparative cost of cryoprecipitate-PR versus plasma-derived and recombinant clotting factor concentrates are limited, but appear to demonstrate savings in some settings (26). With locally prepared VIP S/D cryoprecipitate in Egypt, the cost per unit of factor VIII from cryoprecipitate-PR was US\$ 0.07 compared with US\$ 0.14 for commercial factor VIII concentrates. The average cost per unit of FVIII:C for all types of commercial clotting factor concentrates was higher at US\$ 0.21 (26). The application reported that the current cost per IU of FVIII:C and of von Willebrand factor:RCo for locally prepared VIP S/D cryoprecipitate in Egypt was between US\$ 0.09 and US\$ 0.16 based on the yield per processed pool of 30–35 cryoprecipitates. The cost per gram of fibrinogen for locally prepared VIP S/D cryoprecipitate in Egypt is US\$ 24–29. In Thailand, the current cost per IU of FVIII:C for heat-treated freeze-dried cryoprecipitate was reported to be US\$ 0.11. The cost per gram of fibrinogen for heat-treated freeze-dried cryoprecipitate in Thailand is less than US\$ 51. In comparison, the cost per IU of FVIII:C of an imported commercial clotting factor concentrate made in France is typically more than twice the unit price of locally prepared cryoprecipitate-PR products made in Egypt and Thailand. Similarly, the cost per gram of fibrinogen is US\$ 470, significantly more than the cost for locally prepared cryoprecipitate-PR products made in Egypt and Thailand. In high-income countries, the cost per IU of FVIII:C may be greater for cryoprecipitate-PR than for commercial clotting factor concentrates. For example, in the United Kingdom in 2015, the cost of cryoprecipitate – pooled, methylene blue treated and removed, leukocyte depleted – was reported in the application to be £4.30 per unit of FVIII:C. In comparison, in 2017, the average cost per unit of FVIII:C for commercial clotting factor concentrates was £0.74. This disparity arises primarily from the difference in preparation methods, namely production of cryoprecipitate-PR from single units of plasma in high-income countries versus production from pools of cryoprecipitate in low- and middle-income countries. Differences in the unit costs of labour and materials may also contribute to this disparity.

WHO guidelines

WHO guidelines on the use of cryoprecipitate-PR are not currently available. However, in 2021, WHO announced an initiative to develop guidelines on implementation of patient blood management (20). The WHO Expert Committee on Biological Standardization has developed requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (21), guidelines for viral inactivation and removal procedures intended to assure the viral safety of human blood products (22), and guidelines on the management of blood and blood components as essential medicines (23).

Availability

The application reported that at present, cryoprecipitate has regulatory authorization in Egypt, Thailand and the United States. In Egypt and Thailand, cryoprecipitate-PR is available for replacement of factor VIII and von Willebrand factor (and, based on content labelling, presumptively for fibrinogen). Widespread use of cryoprecipitate-PR as an alternative to industrially fractionated clotting factor concentrates has only been reported in Egypt. Production at one large blood establishment in Cairo has met one third of the annual need for factor VIII replacement in the country through an organized system of distribution. In the United States, cryoprecipitate-PR is authorized only for replacement of fibrinogen complex. The extent to which its use may replace non-pathogen-reduced cryoprecipitate has not been established. In the United Kingdom, cryoprecipitate-PR is recognized for replacement of factor VIII, von Willebrand factor, fibrinogen and fibronectin, but its use is limited to persons born after 1 January 1996, as part of a programme to prevent transmission of variant Creutzfeldt–Jakob disease from blood products.

Other considerations

In 2009, the WHO Blood Regulators Network issued the following position statement on the use of cryoprecipitate-PR in settings where commercial clotting factor concentrates are unavailable or unaffordable (27). "Plasma-derived and recombinant CFC [coagulation factor concentrates] are recognized by relevant professional organizations as the treatment of choice for hemophilia A and von Willebrand disease based on their established quality, safety, efficacy and ease of use. However, resource limitations in many low- and medium-income countries currently make these products unavailable for the vast majority of patients, resulting in significant morbidity and mortality from otherwise preventable bleeding. In these settings, consideration should be given to local production of pathogen-reduced cryoprecipitate made under Good Preparation Practices in blood establishments from pooled whole blood-derived plasma or pooled cryoprecipitates using technologies that have been approved by advanced regulatory authorities. Plasma units obtained as a byproduct of whole blood collection can provide a stable and ongoing local source for preparation of pathogen-reduced cryoprecipitate in an organized and regulated national blood system. Pathogen-reduced cryoprecipitate can also provide a safe source of fibrinogen when used for treatment of fibrinogen disorders in various medical conditions including acquired deficiencies due to massive hemorrhage in trauma or obstetrics. Where feasible, non-pathogen-reduced cryoprecipitate should be replaced by pathogen-reduced cryoprecipitate in the treatment of patients with hemophilia A, von Willebrand Disease and fibrinogen disorders. Pathogen-reduction may be performed on plasma used for the preparation of cryoprecipitate, or on the product itself using a validated method. The residual risk of virus transmission is strongly dependent on the regional virus epidemiology and the screening technology applied. Hence, implementation of a pathogen inactivation technology for cryoprecipitate should not be a substitute for Good Preparation Practices in donor selection, blood collection, laboratory testing for HIV, HBV and HCV and other relevant agents including emerging viruses, product processing, traceability and hemovigilance reporting, as described in WHO recommendations and Guidelines. In line with the recommendation of the World Federation of Hemophilia locally generated pathogen-reduced cryoprecipitate should be regarded as a step-wise improvement in the treatment of patients with bleeding disorders that should not supplant and may coexist with programs to expand patient access to CFC through local or regional plasma fractionation, toll fractionation of domestic plasma or importation of the products. Treatment with cryoprecipitate that is not pathogen-reduced should be discouraged, particularly in the setting of repeated use due to the risk of contamination with blood-borne viruses that is amplified by plasma pooling. Based on these considerations, the WHO Blood Regulators Network advocates use of pathogen-reduced cryoprecipitate in resource limited settings until CFC are available and affordable, subject to a careful assessment of risk and benefits and an organized nationally regulated blood system operating under Good Preparation Practices."

1. The use of essential drugs. Report of the WHO Expert Committee, 1989 (including the 6th Model List of Essential Drugs). Geneva: World Health Organization; 1990 (WHO Technical Report Series, No. 796; <https://apps.who.int/iris/handle/10665/39338>, accessed 6 October 2023).

2. Data & statistics on hemophilia [internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022. (<https://www.cdc.gov/>

ncbddd/hemophilia/data.html, accessed 6 October 2023).

3. Report on the annual global survey 2020. Montreal: World Federation of Hemophilia; 2020 (<https://www1.wfh.org/publications/files/pdf-2045.pdf>, accessed 6 October 2023).
4. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Int Med*. 2019;171(8):540–6.
5. Soucie JM, Miller CH, Dupervil B, Le B, Buckner TW. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia*. 2020;26(3):487–93.
6. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood*. 1987;69(2):454–9.
7. Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr*. 1993;123(6):893–8.
8. Baron JM. Williams hematology. *JAMA*. 1995;274(8):661.
9. Maternal mortality – fact sheet [internet]. Geneva: World Health Organization; 2023 (<https://www.who.int/news-room/fact-sheets/detail/maternal-mortality>, accessed 6 October 2023).
10. Road traffic injuries - fact sheet [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/news-room/fact-sheets/detail/road-traffic-injuries>, accessed 6 October 2023).
11. El-Ekiaby M, Sayed MA, Caron C, Burnouf T, El-Sharkawy N, Goubran H, et al. Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system. *Transfus Med*. 2010;20(1):48–61.
12. El-Ekiaby M, Goubran HA, Radosevich M, Abd-Allah A, El-Ekiaby A, Burnouf T. Pharmacokinetic study of minipooled solvent/detergent-filtered cryoprecipitate factor VIII. *Haemophilia*. 2011;17(5):e884–8.
13. Nuchprayoon I, Sahasittiwat S, Kittikalayawong A, Chantanakajornfung A. Lyophilized cryoprecipitate for children with hemophilia. *J Med Assoc Thai*. 2002;85 Suppl 1:S293–7.
14. Taychakhoonavudh S, Phoolcharoen W, Pesirikan N. The landscape of biologics drug system in Thailand. *J Health Sci*. 2020;29:S96–S111.
15. Guidelines for the blood transfusion services in the UK. Ninth edition. London: Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee; 2023 (<https://www.transfusionguidelines.org/red-book>, accessed 6 October 2023).
16. Package insert. INTERCEPT® blood system for cryoprecipitation. For the manufacturing of pathogen reduced cryoprecipitated fibrinogen complex. Silver Spring, MD: United States Food and Drug Administration; 2021 (<https://www.fda.gov/media/143996/download>, accessed 6 October 2023).
17. Wong H, Curry N. Cryoprecipitate transfusion: current perspectives. *Int J Clin Transfus Med*. 2016;4:89–97.
18. El-Ekiaby M, Burnouf T, Radosevich M, Goubran H. Safety and efficacy of mini-pool S/D cryoprecipitate-poor-plasma (S/D-CPP) in partial volume therapeutic plasma exchange. *Vox Sang*. 2013;105(Suppl 1):65–299.
19. Galas FR, de Almeida JP, Fukushima JT, Vincent JL, Osawa EA, Zeferino S, et al. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. *J Thorac Cardiovasc Surg*. 2014;148(4):1647–55.
20. The urgent need to implement patient blood management: policy brief. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/346655>, accessed 6 October 2023).
21. WHO Expert Committee on Biological Standardization. Forty-third report. Annex 2: requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (revised 1992). Geneva: World Health Organization; 1994 (WHO Technical Report Series, No. 840; <https://apps.who.int/iris/handle/10665/39048>, accessed 6 October 2023).
22. WHO Expert Committee on Biological Standardization. Fifty-second report. Annex 4: guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. Geneva: World Health Organization; 2004 (WHO Technical Report Series, No. 942; <https://apps.who.int/iris/handle/10665/42921>, accessed 6 October 2023).
23. WHO Expert Committee on Biological Standardization. Sixty-seventh report. Annex 3: guidelines on management of blood and blood components as essential medicines. Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1004; <https://apps.who.int/iris/handle/10665/255657>, accessed 6 October 2023).
24. Okerberg CK, Williams LA, 3rd, Kilgore ML, Kim CH, Marques MB, Schwartz J, et al. Cryoprecipitate AHF vs. fibrinogen concentrates for fibrinogen replacement in acquired bleeding patients – an economic evaluation. *Vox Sang*. 2016;111(3):292–8.
25. Novak A, Stanworth SJ, Curry N. Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage – how do they compare? *Expert Rev Hematol*. 2018;11(5):351–60.
26. El-Ekiaby M, Burnouf T, Goubran H, Radosevich M, El-Ekiaby A. Role of the mini-pool cryoprecipitate technology for cost-saving and guarantee of local factor VIII, von Willebrand factor and fibrinogen product supply: Egypt experience. *Ann Blood*. 2018;3:22.
26. Position statement on use of pathogen-reduced cryoprecipitate in settings where commercial clotting factor concentrates are unavailable or unaffordable. Geneva: WHO Blood Regulators Network (BRN); 2009 (<https://www.who.int/publications/m/item/BRN-Position-Statement-on-Pathogen-reduced-Cryoprecipitate>, accessed 6 October 2023).

