A.11	Cryoprecipitate (pathogen-reduced) – bleeding disorders – EML and EMLc
Draft recommendation	☐ Recommended ☐ Not recommended **Justification**: Cryoprecipitate is prepared from Fresh Frozen Plasma thawed at a temperature between 1°C and 6°C, the precipitation of cold-insoluble proteins and the collection of factor concentrates after centrifugation allows the separation of these proteins: fibrinogen, factor VIII, factor XIII, and von Willebrand factor. Thus produced, units are refrozen and stored at -18°C in volumes of 10 to 20 ml of plasma for up to 12 months. The current practice guidelines mandate that cryoprecipitate be transfused after 45 minutes of thawing and be infused within 4 hours. Multiple single donor units of cryoprecipitate (typically 5 or 6 units) are combined into a single pooled unit, thus the risk of viral transmission per dose is actually not acceptable. Cryoprecipitate was used in the 1970s-1990s for the treatment of hemophilia A and various factor deficiencies. In the last 20 years, its use has been increasingly limited to the treatment of haemorrhage with the development of individual factor concentrates. Given current guidelines indicating focus on single factor replacement, cryoprecipitate's role may soon become historical or limited to resource-constrained settings. International guidelines advise use of cryoprecipitate only if fibrinogen concentrates are unavailable. Many clinical guidelines have recommended against cryoprecipitate for replacement therapies for hemophilia A, FXIII deficiency, hypofibrinogenemia and in von Willebrand disease these conditions unless specific factor replacement products are unavailable. As a result, cryoprecipitate is primarily used as a concentrated source of fibrinogen in the setting of acquired fibrinogen deficiencies: massive blood loss from trauma, haemorrhagic obstetric complications, liver transplant .. Cryoprecipitate is still often integral in massive transfusion protocols as a fibrinogen source. It can be utilized when plasma fibrinogen is found to be less than 150 to 200 mg/dL. However, many institutions are moving toward use of fibrinogen concentrate, given ease of use and limited infection risks with this product. Fibrinogen concentrate has many potential advantages including a rapid administration, the predictability of dose response, and a lower risk for viral transmission.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments:** Insufficient access to clotting factor replacement products in low- and middle-income countries leads to early mortality in patients with hemophilia A, von Willebrand disease, and acute massive bleeding. According to the WFH, 75-80% of hemophilia patients have no access to any form of treatment, even in the last three decades. Cryoprecipitate has been used worldwide since the 1960s to replace coagulation factor VIII, von Willebrand factor, and fibrinogen deficiencies (as well as factor XIII) to treat major bleeding in these patient groups. Many clinical guidelines have recommended against the use of cryoprecipitate for replacement therapies in hemophilia A, FXIII deficiency, hypofibrinogenemia, and von Willebrand disease unless specific factor replacement products are not available. As an interim strategy, the lack of access to safe and affordable clotting factor concentrates to treat hemophilia A and von Willebrand disease may be partially addressed by strengthening national blood systems to allow for local cryoprecipitate production.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** Since individual factor concentrates have surpassed cryoprecipitate as front line for replacement therapies for hemophilia A, FXIII deficiency, hypofibrinogenemia and in von Willebrand disease cryoprecipitate is primarily used as a concentrated source of fibrinogen in the setting of acquired fibrinogen deficiencies: massive blood loss from trauma, hemorrhagic obstetric complications, liver transplant, cardiac surgery, and recent studies only addressed those settings. An increase in, or maintenance of, plasma fibrinogen levels following cryoprecipitate administration has been observed in both prospective and retrospective studies in cardiac surgery and trauma. A randomized study evaluated the haemostatic effects of fibrinogen concentrate compared with cryoprecipitate in 63 children following cardiac surgery with cardiopulmonary bypass. There was no significant difference between fibrinogen concentrate and cryoprecipitate groups in the primary outcome of postoperative blood loss during 48 hours after surgery. The posttreatment incidence of allogeneic blood transfusion was also similar. Among women with major obstetric haemorrhage, a retrospective observational study showed an independent beneficial effect on mortality associated with cryoprecipitate administration additional to that of tranexamic acid. Similarly, early cryoprecipitate administration in trauma patients was associated with improved survival in a UK-based, prospective cohort study.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☐ No ☐ Not applicable **Comments:** The risk of pathogen transmission is one of the primary concern with cryoprecipitate. As cryoprecipitate is usually administered as a pooled dose of approximately 10 units from multiple donors, the risk of viral transmission per dose is actually higher compared with fresh frozen plasma. The residual risk of virus transmission is highly dependent on the regional epidemiology and the screening technology applied. Even though allogeneic blood products have been screened since 1985 with nucleic acid testing for viruses such as hepatitis C and human immunodeficiency virus, it is impractical to screen for all viruses or emerging infectious diseases. Pathogen reduction (PR) of blood products renders any source containing nucleic acids incompetent for replication through various pathogen reduction technologies. PR has recently been adapted to the use of cryoprecipitate; it can eliminate major risks associated with blood borne infectious agents.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable **Comments:** With any allogeneic transfusion, including cryoprecipitate, there is a risk of alloimmunization and allergic transfusion reaction. Transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and allergic transfusion reactions remain significant risks and are associated with increased health care cost, morbidity, and mortality. Although the adverse-event rate with cryoprecipitate is difficult to quantify precisely, one hemovigilance study of adverse transfusion events reported a rate of 6.57 events per 10,000 units administered. This is considerably lower than rates reported for all other blood components evaluated, including for fresh frozen plasma.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: validated technics and devices for pathogen reduction should be available
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Data on the comparative cost of Cryo-PR versus plasma derived and recombinant clotting factor concentrates are limited, but appear to demonstrate significant savings in some settings. For exemple an imported commercial clotting factor VIII concentrate is typically more than twice the unit price for locally prepared Cryo-PR products made in Egypt and Thailand. Fibrinogene concentrate is often perceived as much more expensive than cryprecipitate. However, the true cost of cryoprecipitate may not be directly seen. Saving are made with fibrinogen concentrate as there is no need for compatibility testing, or thawing and administration is simpler. The cost should also include the pathogen reduction process.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable **Comments**: Detergent Virus Inactivation kits and the device manufacturer have to be recognized and approved by the regulatory authority

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable **Comments:** There is a Position Statement by WHO Blood Regulators Network (BRN) on Use of Pathogen-Reduced Cryoprecipitate in Settings Where Commercial Clotting Factor Concentrates are Unavailable or Unaffordable