To whom it may concern,

I wish to comment on the Expert Review No. 2 regarding addition of Whole Blood and Red Blood Cells to the WHO EML. I am a clinical hematologist by training and have had direct patient responsibility for patients with hematologic disorders including hemoglobinopathies, bleeding disorders, and malignancies. For more than 35 years I have directed collection and preparation of blood components and chaired and served on numerous committees that develop standards for the medicinal use of blood. I am a member of the Transfusion and Trauma Committee of the US Department of Defense. I am concerned that despite the well-documented discussion of the studies of the use of blood and its risks and benefits, that Expert No. 2 recommends deferring a decision in order to “identify additional clinical evidence.” Such a deferral will delay unnecessarily the advancement of safe transfusion therapy in countries that need it most and will do nothing to reduce the burden of disease that safe transfusion of Whole Blood and Red Cells can effect.

**Efficacy of Whole Blood and Red Cells**

As the Expert notes, the efficacy of Whole Blood and Red Cells is universally recognized and accepted. Studies of severely anemic patients or bleeding trauma victims cannot be randomized to those who are permitted to be transfused versus non-transfused controls. Such studies would be unethical precisely because the efficacy of Whole Blood and Red Blood Cells is universally acknowledged. Patients who need transfusion die without it. As with most medicines, however, controversy still exists regarding all indications, precise determinants for initiating therapy, and precise dose for each indication. This is true for virtually all medications and is usually addressed with “labeling” as is the case with the numerous guidelines (referenced in the application) for the use of these products. As the Expert indicates, it is unclear whether children with haemoglobin levels of 5-6 g/dL require transfusion, however the literature is crystal clear that below these levels, children with
malaria die without transfusion, as do patients who refuse transfusion for religious reasons. No additional studies in this area will be forthcoming nor can they be done.

As the Expert notes, the literature regarding transfusion practice is vast and there is sufficient evidence that blood transfusion is effective in numerous circumstances. Many of the experts’ cited studies (e.g. TRICC) do not address efficacy, but rather dose of drug. The numerous meta-analyses of retrospective studies do not negate the efficacy of blood, but rather, as the Expert alludes to, recognize that the most patients who require transfusion are ill and many die. For ethical reasons, none of these studies has an untransfused control group. Such studies will never be performed. The closest study, cited by the Expert, the CRIT study, compared red cell transfusion with the far more expensive medication, recombinant erythropoietin, and found no difference in efficacy or safety (both were judged safe and effective; neither was superior, but the recombinant biologic was far more costly). The Expert must separate the “product” from the practice and the product, when appropriately manufactured is clearly acknowledged as effective.

**Safety**

There is likewise a voluminous literature on the safety of blood; it is likely the longest and best studied medicine in terms of adverse events. It is true that the product may vary from country to country. One advantage of placing these products on the EML is to emphasize that when blood is appropriately manufactured, that is, treated like the medicine it is, (applying quality assurance processes and GMP) safety is not only improved but is very high. It is important to note that several of the studies cited by the Expert (Marik and Corwin etc) did not conclude that the risks of blood administration outweighed the benefit. These (primarily retrospective) analyses concluded that there was an association between red cell administration and a variety of adverse events, once again confirming a) that patients who receive blood are usually sicker than those who do not; b) those who receive more blood are usually sicker than those who receive less blood; and c) that adverse events associated with blood administration are more likely to occur in those that receive more blood. Once again, one cannot conduct a study in which patients are not transfused when a physician deems that transfusion is indicated—an century of experience and a large literature confirm that it is unethical to do so. There are no randomized, controlled trials of the safety of red cell transfusion, only trials comparing one level of transfusion with another.

**Cost**

As the Expert indicates cost varies from country to country as it does with many medications. However blood is available at reasonable cost in most countries in the world. There is no less costly alternative. In fact, there is no alternative medication.

Finally and importantly, it is critical to separate blood products as a medicine from controversies about commercialism. The WHO endorses voluntary unremunerated donation; it has for decades. This position can be emphasized in a footnote or further addressed by individual Member States with policy or legislation. Religious objections to receiving blood (or any medication) are valid, but unrelated to the recognition of blood products as medicines. Many patients also refuse vaccines. There is no evidence whatsoever that adding blood to the EML will encourage commercialization. Adding blood to the EML underscores the importance of appropriate production, oversight and use of this lifesaving
medicine. It would be a shame to delay a decision in the hope or expectation that “additional clinical data” will be provided for a medicine that is universally acknowledged as effective and safe and recommended by numerous WHO consultations, committees, and publications when prepared and administered in accordance with recognized guidelines. This has been emphasized repeatedly by the World Health Assembly. Most practicing physicians are astonished to learn that Whole Blood and Red Cells are not already considered Essential Medicines by the WHO. To delay a decision is to miss an opportunity to improve the quality, safety, availability and accessibility of a truly essential medicine in Member States that need such an endorsement to upgrade developing blood services. I encourage the Committee to take the appropriate action.

Yours truly,

Harvey G. Klein M.D.
Chief, Department of Transfusion Medicine
Clinical Center
National Institutes of Health