Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic

Interim guidance for ethics review committees, researchers, national health authorities and blood transfusion services

World Health Organization

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1. Background

WHO convened a Consultation on Potential Ebola Therapies and Vaccines in Geneva, Switzerland on 4–5 September 2014. In the absence of proven treatments, participants widely agreed that convalescent whole blood and convalescent plasma, among other experimental interventions, should be considered for use for people with Ebola virus disease. Any such use should be scientifically studied through carefully designed research studies. If, however, convalescent whole blood and convalescent plasma are used for treating people with Ebola virus disease outside research studies, this use should be considered "monitored emergency use of unregistered and experimental interventions", a term coined by WHO in the context of the current Ebola outbreak to refer to an exceptional use of experimental interventions outside clinical trials, and to reflect the urgent need to collect data on their efficacy and safety *(1,2).*[1]

This document specifically analyses the ethical issues surrounding the potential use and study of convalescent whole blood and convalescent plasma in both research and clinical settings.

2. Ethically relevant facts

2.1 Context constraints

The Ebola epidemic is occurring in countries in western Africa that are not adequately prepared to respond. Standard operating procedures for using convalescent whole blood and convalescent plasma among people with Ebola virus disease do not exist. The current situation in the affected countries is as follows.

- They lack the functional health care systems necessary to treat the people who are sick and adequate public health systems and personnel to prevent the spread of Ebola virus disease.

- There is poor public understanding of Ebola virus disease, which has sparked rumours and fears about its causes and treatment and has led to a lack of compliance with recommended infection control practices, such as safe burials.

- There is an insufficient number of health-care workers to provide care. These countries faced critical human resource shortages in the health sector before this outbreak, and Ebola virus disease has taken a high death toll on this population subgroup: health-care workers who become infected have an estimated case fatality rate of 59% *(3)*. This critical shortage, the lack of adequate training and protective equipment for health-care workers and the widespread public distrust of health officials and health-care workers tremendously affect their commitment to work and reduce the number of health-care workers per capita. This further complicates efforts to control the epidemic.

- The availability of basic blood transfusion services in some of the affected countries could ease the use of convalescent whole blood or convalescent plasma for Ebola virus disease. However, collecting, processing and using convalescent whole blood and convalescent plasma are more challenging than routine blood transfusion activities because of (1) the risks associated with contact with people with Ebola virus disease during blood transfusion and (2) the difficulties of maintaining a registry of people with Ebola virus disease who have recovered, especially those

[1] Monitored emergency use of unregistered interventions may be achieved through existing regulatory mechanisms that contemplate the use of unregistered interventions under specific emergency circumstances, such as the notion of emergency use of an investigational new drug by the United States Food and Drug Administration.

who live in remote and hard-to-reach areas and (3) the limited feasibility of obtaining blood or plasma donations from donors in the midst of overwhelmed health-care systems with limited infrastructure capacity and human resources.

2.2 Uncertain therapeutic efficacy of convalescent whole blood and convalescent Plasma for people with Ebola virus disease

It is unknown whether convalescent whole blood and convalescent plasma can effectively treat patients with Ebola virus disease. There is theoretical reason to expect that antibodies in the blood or plasma of individuals who have survived Ebola virus disease would reduce the viral load of individuals who are acutely ill due to the virus, but this remains unproven.

Transfusion of immune plasma is a standard therapy for South American haemorrhagic fevers caused by arenaviruses, and it has been used successfully for treating people infected with other infectious agents *(4)*. For instance, in Hantavirus infection, convalescent plasma was safe and reduced the case fatality rate to 14% in 29 treated cases versus 32% in 199 untreated cases *(5)*. Nevertheless, only anecdotal evidence suggests the possible efficacy of convalescent plasma *(6)*, and evidence of the efficacy of convalescent whole blood among patients with Ebola virus disease is disputed *(7,8)*. Some existing experimental data have even indicated the absence of efficacy of immune plasma and of whole blood transfusions in non-human primates infected with various filovirus strains (which include Ebola viruses) *(9–11)*. However, monoclonal antibody cocktails *(12–14)* and immunoglobulin preparations from vaccinated and challenged monkeys *(15)* have been effective in preventing Ebola virus disease and treating monkeys with Ebola virus disease in the monkey challenge model.

2.3 Uncertain therapeutic safety of convalescent whole blood and convalescent plasma for people with Ebola virus disease

The safety of convalescent whole blood and convalescent plasma therapies for people with Ebola virus disease is not fully known, and there is a theoretical concern and some experimental evidence about antibody-dependent enhancement of Ebola virus infection when these therapies are used in cell culture *(16)*. However, the use of convalescent whole blood and convalescent plasma for other conditions is generally considered safe if standard precautions *(17)* and blood safety strategies are effectively implemented, such as screening donated blood for transfusion-transmissible infections. Thus, if these precautions and strategies are followed, and donors are people who have fully recovered from Ebola virus disease *(18)*,[2] transfusing convalescent whole blood or convalescent plasma for treating patients with Ebola virus disease is expected to be safe.

2.4 Medical and psychosocial condition of convalescent people

People convalescing from Ebola virus disease often remain ill for weeks after recovering from the acute phase: residual fatigue, poor nutritional status and joint pain are common *(19)*. More severe complications can also be seen, associated with immune recovery *(20,21)*.

In addition, they may be affected by long-lasting mental distress because of the trauma of isolation in Ebola treatment facilities, survivor's guilt, social stigma, the loss of relatives or close friends, material losses and rejection by their community *(22–25)*.

[2] To be released from care and eligible to donate, these patients should have a negative result on reverse-transcriptase polymerase chain reaction (RT-PCR) on two blood samples (drawn 48 hours apart).

All these conditions make convalescents especially vulnerable to even slight coercion or to additional physical burdens if blood donations are to be considered.

3. Ethical analysis and recommendations

The WHO Ebola Ethics Working Group emphasizes that priority should be given to providing basic supportive care to everyone with Ebola virus disease and to preventing the spread of the epidemic. For the sake of efficiency, and to maximize the benefits of efforts, interventions with known benefits should be given priority. In the context of experimental interventions, for the sake of fairness, priority should be given to studying promising interventions that (if proven to be safe and effective) could reach the most affected individuals and prevent the greatest number of people from becoming infected or save the lives of people with Ebola virus disease. Given the high mortality resulting from Ebola virus disease and the absence of proven cures and vaccines, providing people with a potentially beneficial intervention – such as convalescent whole blood or convalescent plasma – is ethical, even if its efficacy is unknown *(1)*. The ethical acceptability of providing convalescent whole blood or convalescent plasma is partly supported by the presumed positive risk–benefit balance of these therapies when standard blood safety strategies are being implemented – that is, the risks of negative side effects are considered low when blood safety measures are in place, and theoretical and some anecdotal evidence indicates that people with Ebola virus disease may benefit from these therapies. In addition, the WHO Ebola Ethics Working Group considers that the following issues are ethically relevant in providing convalescent whole blood and/or convalescent plasma to people with Ebola virus disease.

3.1 Gathering evidence

In its deliberations on 21–22 October 2014, the WHO Ebola Ethics Working Group reiterated that *(2)*:

> There is an ethical imperative to carry out research on potential therapeutic agents against Ebola virus disease.
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> Even in the context of a public health emergency, unregistered and experimental drugs and therapeutics must be tested for safety and efficacy using rigorous methods and simple but properly designed clinical trials. In the context of the current Ebola epidemic in West Africa, WHO has already published recommendations that it is ethical to make investigational therapeutics available outside of clinical trials for "emergency use" provided clinical data from their use is systematically collected and shared. Such "emergency use" should not preclude or delay the initiation of more conclusive investigations of the intervention in properly designed clinical studies. The latter, if appropriately designed and executed, may yield generalizable conclusions that result in greater societal benefit.
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> The WHO Ebola Ethics Working Group proposed that the term "monitored emergency use of unregistered and experimental interventions (MEURI)" should be used in this case instead of "compassionate use" – a term that can have other meanings, such as use of an investigational intervention for patients outside of an ongoing clinical trial or the indicated scope of utilization.

It is therefore ethically imperative to learn whether convalescent whole blood and convalescent plasma are safe and efficacious for treating people with Ebola virus disease through carefully designed and executed research studies. All efforts must be made to systematically gather relevant data. This includes collecting safety data from transfusions of convalescent whole blood and convalescent plasma, whether under research or monitored emergency use of unregistered and experimental interventions, analysing these data and making them publicly available in an expedited manner without compromising standard and supportive care, donor or recipient confidentiality or

health worker safety. Most crucially, immediate action should be taken locally and internationally to respond to the new risk–benefit information that results from research related to convalescent whole blood and convalescent plasma and to other experimental Ebola interventions. Examples include closing clinical trials or treatment in the context of monitored emergency use of unregistered and experimental interventions if relevant evidence is presented of harm to the donor or the person with Ebola virus disease.

3.2 Disseminating results

Whether such treatment is successful or unsuccessful and whether it is part of research or monitored emergency use of unregistered and experimental interventions, the results should be disseminated as widely as possible to maximize their value in the Ebola epidemic. An important priority in the dissemination plan is to provide for communication in a differentiated form with all relevant audiences, including donors, people with Ebola virus disease receiving convalescent whole blood or convalescent plasma, clinical practitioners and the wider public. People with Ebola virus disease and other stakeholders should also be updated as the trial proceeds and promptly informed on the results obtained.

3.3 Community engagement[3]

Engagement with local communities may be challenging in the context of the Ebola epidemic but is of paramount importance to ensure fair processes in developing and implementing convalescent whole blood or convalescent plasma programmes. This means that stakeholders should have a fair opportunity to participate in deliberations about the future of the community and in the decisions that may affect their lives. Communities should understand the rationale behind interventions with convalescent whole blood and/or convalescent plasma, be involved in developing these programmes and be able to decide whether these therapies are locally acceptable. Community engagement should start early and be as inclusive as possible. The role of families in engagement practices should also be considered, especially since they may be able to offer even more compelling reasons for individuals to cooperate with their community and health systems. However, familial coercion is a concern and should not be ignored (see section 3.6.1).

Community engagement processes need to identify the best ways of conveying not only the uncertainty inherent in research but also seemingly contradictory messages: that contact with the body fluids of a person with Ebola virus disease will transmit the disease and must be avoided, but transfusion of blood from someone who has recovered from Ebola virus disease is safe, if the donors' blood is properly screened for infections and is compatible with that of the recipients, and might help