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LETTERS

EBOLA

Ebola virus vaccine trials: the ethical mandate for a therapeutic safety net

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Randomised controlled trials (RCTs) offer the fastest and most rigorous assessment of vaccine efficacy.[1] But they are ethical only if there is "clinical equipoise"—genuine uncertainty in the medical community about whether the experimental intervention will do more good than harm.[2] We argue that Ebola virus vaccine RCTs can achieve clinical equipoise without sacrificing scientific rigour by providing trial participants who develop Ebola virus disease (EVD) with enhanced supportive care and access to experimental therapeutics.

Most discussions have analysed Ebola vaccine and treatment RCTs under a single ethical framework, noting that EVD's high case fatality rate undermines equipoise for even slightly promising interventions.[3] Yet there is a crucial distinction: treatment RCTs investigate whether experimental treatments prevent death, whereas vaccine RCTs investigate whether experimental vaccines prevent disease. Consequently, efforts to achieve equipoise by minimising the case fatality rate would impede efficacy assessment in treatment RCTs but not vaccine RCTs. Thus, scientifically valid vaccine RCTs can and should minimise mortality risk by providing the best standard of care, including access to experimental therapeutics, for any trial participant who develops the disease (figure⇓).

Although patients treated to date with experimental drugs and convalescent blood products differ from other patients in important ways, suggestive evidence links these treatments to better outcomes (table⇓). More importantly, the consistent use of experimental treatments in the US and Europe implies that the health community expects their benefits to outweigh potential side effects.

Including a "therapeutic safety net" in vaccine RCTs would facilitate clinical equipoise and fulfil the ethical mandate to provide trial participants with the standard of care in the sponsoring countries.[8] Proposed Ebola vaccine RCTs anticipate they will reach their stopping criteria after only 30-60 infections.[9] Thus, the supportive care infrastructure and supplies of drugs or blood products needed to establish a therapeutic safety net should be attainable.

Competing interests: None declared.

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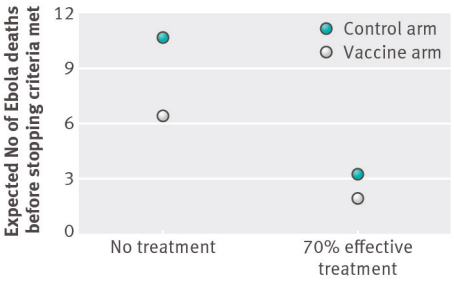
Table

Table 1| Case fatality rates for Ebola according to treatment, restricted to younger age groups to control for age associated variation in survival

Type of study (region)	No of deaths	Case fatality rate (%) (95% CI)	Age (years)
Experimental therapeutics and intensive supportive care (Europe and North America)*	0/6	0 (0 to 46)	19-40
Intensive supportive care (Guinea)[5]	4/19	21 (8 to 55)	19-40
Intensive supportive care (Sierra Leone)[6]	27/35	77 (60 to 90)	21-40
Intensive supportive care (pooled)[5 6]	31/54	57 (43 to 71)	19-40
All cases with definitive outcomes (Guinea, Sierra Leone, Liberia)[7]	577/838	69 (66 to 72)	15-44

*Collected from available media reports as of 26 November 2014.

Figure



Anticipated number of deaths among participants by trial arm in a hypothetical vaccine trial, with and without a treatment that reduces the case fatality rate by 70%. The therapeutic safety net reduces overall mortality and, crucially, also substantially bridges the gap between the two arms, thereby facilitating clinical equipoise. Following vaccine trial proposals,[4] we assume that 30 participants will become infected before the trial reaches its stopping criteria. All assumptions are explained in the supplementary code (http://ebola.ici3d.org/BMJ/equipoise.R)