Survival benefits associated with neonatal clinical trial participation in a resource-limited setting: Quantifying the “healthy trial effect”

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Randomised controlled trials (RCTs) conducted in resource limited settings (RLS) are essential for context-specific evaluation of new health interventions. RCT implementation and involvement is also recognised to have direct benefits for participants, so called “healthy-trial effect”. However, there is a lack of precise data quantifying the survival benefits for vulnerable populations in the highest burden, lowest resource settings and this is essential for RCT design and to inform the ethical risk-benefit debate. This prospective observational study was embedded in a RCT investigating the survival effect of KMC prior to stability (eKMC trial), conducted at the only teaching hospital and neonatal referral unit in The Gambia (2018 – 2020). All neonates <2000g and <24h old admitted during the trial recruitment period underwent clinical assessment, socio-demographic data collection and prospective recording of in-hospital all-cause mortality. Neonates meeting protocol eligibility criteria of mild-moderate instability were classed as either recruited (group A) or not recruited due to lack of study bed, unavailable caregiver or declined consent (group B). Between-group differences in socio-demographic and clinical variables were explored using Wilcoxon-Mann-Whitney test (continuous variables) and Chi squared test (categorical variables). The in-patient case-fatality rates of both groups were then compared using an adjusted generalized linear model (binomial variance, log link). 563 neonates were included in the analysis with outcome data available for 547. Baseline clinical and socio-demographic variables were similar between groups, except for differences in twin status, admission age and referral site. In-patient mortality was 22.6% (63/279) in trial participants (group A) versus 29.1% (78/268) in clinically eligible non-recruited newborns (group B), with trial participation associated with 29% relative risk reduction in mortality (aRR 0.71, 95% CI 0.53 – 0.96, p = 0.026). Clinical trial participation is associated with substantial survival benefits for small vulnerable neonates on a resource-limited neonatal unit. This has value for future neonatal trial designs, including sample size estimations, and may prevent research wastage by avoiding underpowered trials. It may also provide insights to improve the quality of small and sick newborn care and supports the ethical imperative for more context specific global newborn health research in RLS.