





Questioning the ethics of international research on formula milk supplementation in low-income African countries

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Over the past three decades, the increase in funding for priority public health issues largely affecting low/middle-income countries (LMICs) has led to the growth in international research involving researchers or research sponsors from a high-income country (HIC) conducting research in LMICs. The ethical considerations in such international research were raised in the 1990s and several ethical guidelines specifically addressing international research were published.^{1 2} However, in 2022, we still find examples of research undertaken by HIC principal investigators and funders, with no benefit and large potential for harm, being undertaken in LMICs.

A randomised controlled trial that began recruiting in February 2021 is nearing completion in Uganda and Guinea-Bissau³ of formula supplementation of breastfed newborns for 30 days, beginning within 6 hours of birth. The primary objective of this trial is to evaluate the efficacy of formula supplementation among low birthweight (LBW) infants <2500 g <6 hours of age and those not LBW with weights <2600 g at 4 days of age. The trial compares breastfeeding and formula (up to 59 mL administered daily) through 30 days of infant age to frequent exclusive breastfeeding (EBF) without supplementation. The hypothesis is that formula increases weight-for-age z-score (WAZ) at 30 days of age (primary outcome) among high-risk infants. Secondary outcomes are weight-for-length z-score (WLZ) at 30 days of age, WAZ, WLZ and length-for-age z-score through 6 months of age, breastfeeding duration and abundance of *Bifidobacterium infantis* in the intestinal microbiota at 30 days of age.

The trial is taking place at Simão Mendes and Cumura Missionary Hospitals in Bissau,

SUMMARY BOX

- ⇒ The increase in funding for priority public health issues largely affecting low/middle-income countries (LMICs) has led to the growth in international research involving researchers or research sponsors from a high-income country conducting research in LMICs.
- ⇒ Several ethical guidelines specifically addressing international research have been published, yet we still find examples of research undertaken by high-income country principal investigators and funders with no benefit and large potential for harm, being undertaken in LMICs.
- ⇒ In this commentary, we provide an example from a trial of formula milk supplementation in Uganda and Guinea-Bissau and outline ways in which this trial violates basic ethical principles and human rights and has zero potential for scale-up within the research settings.
- ⇒ Appropriate, safe and scalable alternatives to formula milk supplementation of low birthweight newborns should be prioritised including zero separation of mothers and newborns, lactation support and human milk banks.
- ⇒ We challenge LMIC institutional review boards, research funders, clinicians, scientists and governments to carefully consider potential maleficence, especially if an intervention is not scalable locally, and exercise their responsibility to protect their citizens from unethical international health research.

Guinea-Bissau and Kawempe Hospital in Kampala, Uganda. Women delivering in the participating hospitals will be screened by local clinicians for having singletons in the eligible weight range 2000–2885 g and following informed consent, randomised on day 0 (if <2500 g) or day 4 (if <2600 g) and have not lost >10% of their birth weight. The intervention group receives breastfeeding combined with up to 59 mL of individually



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prepackaged, single-use, liquid, iron-fortified, human milk oligosaccharide-containing formula (Similac Pro-Advance) administered daily for 30 days. The control group receives standard of care which is a recommendation to EBF for 6 months.³ The trial is funded by the Bill and Melinda Gates Foundation.

This trial raises several ethical issues including beneficence, informed consent and justice. There are also major human rights concerns. The Convention on the Rights of the Child, which both Guinea-Bissau and Uganda have ratified, recognises the right of the child to the enjoyment of the highest attainable standard of health including the right to adequate food.⁴ The protection of breastfeeding is vital to the realisation of these rights.⁵

In this commentary, we outline ways in which this formula supplementation trial violates basic ethical principles and human rights, and we challenge institutional review boards (IRBs), research funders, clinicians, scientists and governments to fulfil their duties to protect their citizens and turn the tide of unethical international health research.

There is overwhelming evidence of the benefits of breastfeeding, especially EBF, for mothers, children and societies.⁶ Uganda and Guinea-Bissau are two of few countries to have achieved the global nutrition target of at least 50% EBF by 2025 with rates of 66% and 59%, respectively.⁷ Declines in breastfeeding rates in these countries would be disastrous for child survival given the high levels of poverty and already high under-5 mortality rates of 46 and 78 per 1000 live births, respectively.⁷ Yet within these contexts, this trial introduces formula milk to mothers and their newborns, with potentially disastrous effects for the participants and their communities. In this case, the protocol is *in direct conflict with international public health breastfeeding recommendations*,⁸ and national nutrition guidelines in both countries.^{9 10}

The *study is uncalled for*. There are existing nutrition guidelines in both countries outlining the management of LBW infants which include breastfeeding counselling and support, kangaroo mother care, breast milk expression and donor human milk. The researchers provide no justification for why the current recommendations should be modified. Therefore, the hypothesis behind the trial reinforces the myth that formula milk is necessary and that breast milk is inadequate for infant nutrition. A recent multicountry study of formula milk marketing found that marketing messages from formula milk companies reinforce these myths which become internalised by women and health professionals.^{11 12}

There is *zero potential for scale-up of the intervention*, irrespective of the trial findings, due to the single-use, individually packed, premixed, hospital-distributed bottles, the risks involved in widescale supplementation of newborns in the public health system, the wide-ranging negative spill-over effects that would undermine breastfeeding practices and the negative environmental impact. Therefore, in this instance, the benefits of the research accrue

entirely to the scientists and potentially to Abbott Laboratories, the formula manufacturer.

The *issue of beneficence* is critical in the case of this study. The ethical principle of beneficence is interpreted as (1) do not harm and (2) maximise possible benefits and minimise possible harms. First, in order to recruit women and follow the study procedures, the participating hospitals will act as formula distributors, which is contrary to the WHO Baby Friendly Hospital Initiative 10 steps to successful breastfeeding.¹³ Second, the study uses premixed individual bottles with teats, which is known to interfere with breastfeeding. The use of such a large volume of formula supplementation (59 mL) in the first days post partum will inhibit the establishment of breast milk production. Breast milk transfer over the first 6 days post partum has been found to range from less than 10 mL/kg body weight on day 1 to around 90 mL/kg body weight by day 4, hence an additional 59 mL formula supplementation constitutes a significant volume increase.¹⁴ The trial completely overlooks the risk of breastfeeding challenges after the formula milk supplementation ends at 30 days, which could potentially have serious negative consequences. There is a risk that participants would seek to purchase formula milk for their infants to continue the supplementation, which since given by health professionals is likely to be viewed as being endorsed by them and having a health benefit for their infants. This would be a major financial burden for women in these contexts of extreme poverty and a major health risk to infants since around 40% of households in both countries do not have access to basic drinking water services.⁷ In many cases where a mother's breast milk production has been negatively affected, the only way the family might be able to continue supplementation will be with unsafe alternatives such as cow's milk, unsafe formula or formula mix, and unclean water and utensils. Low literacy may also impact on the safety of any breastfeeding supplements given. The trial overlooks all of these risks.

Considering the *issues of informed consent*, we question the appropriateness of seeking informed consent for an intervention, such as formula milk supplementation, from a mother within 6 hours of delivery. This does not provide sufficient time for the mother and/or father to make an informed decision regarding the risks and benefits of participation. It could also be argued that requesting permission from a mother to provide a free formula supplement to her newborn within 6 hours of birth, moreover by a health professional, constitutes an undue inducement and that a truly voluntary and informed consent is not possible in these circumstances. Furthermore, randomisation at 6 hours does not provide sufficient time to judge whether supplementation is needed based on any existing clinical criteria. At this time point, a mother is particularly vulnerable and may even be unwell herself. To our knowledge, no consideration was given to systematically confirm her participation at a later time, when she is better able to receive and consider the information provided.

Considering the *role of formula milk*. Human breast milk is vital for infants' growth and survival. The WHO

recommends EBF for 6 months for all infants, with continued breastfeeding for 2 years or more.⁸ In preterm and LBW infants, evidence from systematic reviews in HICs shows that compared with formula milk, human breast milk reduces the risk of developing sepsis and necrotising enterocolitis (NEC), two life-threatening diseases.^{15 16} It has also been shown to protect against retinopathy of prematurity,¹⁷ childhood infections, overweight and obesity, and to improve cognitive performance indicators.¹⁸ Abbott Laboratories, the manufacturer of Similac, is currently facing a lawsuit by parents for failure to warn against the risk of NEC for premature infants fed their formula products.¹⁹ Therefore, optimal breastfeeding practices should be encouraged wherever possible and suitable for preterm infants. When breastfeeding is not feasible, mothers should be supported in lactation, breast milk expression and feeding of their own breast milk to their infant before considering formula milk.⁹ Why therefore is this trial not considering these intermediate steps and jumping to formula milk supplementation?

In terms of justice, one must consider who ought to receive the benefits of research and who bears its burdens. The study is at best likely to demonstrate that excess energy may increase weight, but this disregards the fact that it is still not a viable, scalable nutrition intervention. The larger considerations are the training of health professionals to identify, recruit and distribute formula milk in bottles with nipples to newborns in complete violation of the code and national guidelines. The damage of such scaled up actions will take years to reverse as we saw in South Africa with free formula distribution through health facilities.²⁰

In general, academic institutions in LMICs are highly dependent on research grants and international collaborations to survive in the context of minimal domestic funding. This places them in vulnerable positions in the asymmetry of power and decision-making.²¹ Similarly, local IRBs may face pressures to approve research that is accompanied by large grants even when the risks to the participants are clear. There is a need to put citizens before corporate research ecosystems²²—to see the bigger picture beyond the grams of weight gained and consider lifelong, societal benefits and environmental impact of science.

There is a huge need to improve pregnancy, delivery and newborn services, including maternal and newborn nutrition. In order to achieve that, we can do what we know works including improving maternal nutrition, supporting and protecting early and exclusive breastfeeding and breastfeeding on demand, skin-to-skin contact and continued lactation support.²³ Evidence from LMICs shows that keeping the mother and newborn together from birth with zero separation has huge benefits including improved survival, reduced infections and hypothermia, and earlier initiation of breastfeeding.²⁴ In LMICs, there is an urgent need to increase provision for the mothers of preterm and LBW newborns to stay with their infants. Also, frequent monitoring of children

including capturing any clinical vulnerability, growth stagnation or feeding difficulty is paramount. This requires implementation of interventions that are scalable and currently recommended, and investigation of sustainable and affordable alternatives. Great gains are being made in establishing human milk banks in LMICs, a comparatively safe and affordable intervention.²⁵

We call on the IRBs that approved this trial to re-review if this trial can be justified in view of the ethical and human rights concerns raised above, and we call on the University of California, San Francisco IRB to publish a public statement with their justified final decision.

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