



The COLLABORATE Study: Discretionary Fortification Guidance

We are grateful for the dietetic expertise of the Neonatal Dietitians Special Interest Group that contributed to drawing up this guidance.

1. Summary of the rationale for COLLABORATE randomisation 2 (for a detailed description of the rationale for COLLABORATE, please refer to the full study protocol available on the study [website](#)).

COLLABORATE randomisation 2 is designed to resolve the uncertainty around whether **routine** protein-carbohydrate fortification of human milk feeds is safe and beneficial.

- Routine fortification can achieve faster short-term growth, but no randomised trial to date has shown any benefit on long-term growth, bone health, or neurodevelopment (1)
- Routine fortification could deliver a protein intake of greater than 3.5g/kg/day which may be a risk factor for adverse neurodevelopment and metabolic health (2)

2. Faster growth is not necessarily better growth

Regardless of feed type (unfortified human milk, fortified human milk, formula supplemented human milk), healthy, very preterm babies surviving without major morbidity, converge to follow intrauterine growth **velocity** (3, 4). Most babies born preterm will have experienced a degree of fetal growth restriction. Therefore, an extremely preterm baby following intrauterine **velocity** will weigh less at term-equivalent age than a baby born at full-term and will be below birth centile.

The optimum rate of growth following preterm birth is unknown. However, striving for a baby born very preterm to reach the size of a baby born at full-term, as depicted by current birth weight charts (incorrectly termed “growth” charts) is to promote growth at a rate greater than intrauterine velocity (accelerated growth). Most extremely preterm babies have suffered some degree of fetal growth restriction. Accelerated growth, especially after a period of growth restriction, is also a risk factor for adverse cardiometabolic health.

3. Non-nutritional benefits of Own Mother’s Milk

To maximise the benefits of the non-nutritional components, the aim in COLLABORATE is to promote maximum availability of Own Mother’s Milk aiming for a total human milk (Own Mother’s Milk and pasteurised Human Donor Milk) of up to 200ml/kg/day. This volume is readily tolerated by the majority of extremely preterm babies and is widely used in the UK (5).

4. COLLABORATE safety monitoring

COLLABORATE is a UK Health Research Authority approved 2-randomisation trial, funded by the Department of Health through the National Institute of Health Research. Participants in randomised controlled trials such as COLLABORATE receive careful monitoring over and above that received in the course of normal clinical care.

Study data will be evaluated at intervals by an independent Data Monitoring Committee established by the National Institute of Health Research. The remit of the Data Monitoring Committee is to assess accumulating study data in relation to primary and secondary outcomes (see full protocol for a full list) and any adverse reactions (untoward responses to a study intervention notified by site Principal Investigators) and advise the Trial Steering Committee on early discontinuation if evidence of harm emerges, or conclusive evidence of benefit.

5. When to consider discretionary fortification

5.1 Experience from the COLLABORATE feasibility study, PREMFOOD, indicates that the need for rescue fortification is likely to be minimal (6). However, clinicians may consider discretionary use of fortifier in babies participating in COLLABORATE randomisation 2 if the following conditions apply:

- If after regaining birth weight, and receiving a human milk intake of 180ml/kg/day or more, a baby shows a persistent downward crossing of anthropometric centiles over a ten-day period on the UK Neonatal and Infant Close Monitoring growth chart

AND

- The trend in blood urea is falling, with a value below 1.5 mmol/l indicating no protein excess and likely protein deficiency

AND

- Chronic sodium depletion has been excluded: this is manifest by a slowing of weight gain despite a human milk of 180ml/kg/day or more

**Note: the serum sodium concentration in early deficiency will be normal (7). The urinary sodium concentration is generally unhelpful in evaluating the possibility of sodium depletion in extremely preterm babies. The diagnosis may be corroborated if an initial sodium supplement of 2 mmol/kg/day administered in divided doses results in an immediate increase in weight. The amount of subsequent sodium supplementation required will be influenced by several factors including gestational age and renal maturity, diuretic treatment, and sodium content of feeds.*

AND

- There is no severe intercurrent illness

5.2 Discretionary fortification may also be considered if

- A baby is unable to tolerate a human milk volume of 180ml/kg/day (e.g., treatment resistant gastro-oesophageal reflux; high output stoma)

AND

- The conditions above under 5.1 apply

6. Trial procedures

We ask that any use of rescue fortification and the reasons are documented in the COLLABORATE eCRF and entered into the daily details of the baby's Electronic Patient Record.



Clinicians considering rescue fortification are requested to discuss this with the clinical Chief Investigator (Professor Neena Modi; n.modi@imperial.ac.uk) or Co-Investigator (Dr Sabita Uthaya; s.uthaya@imperial.ac.uk).

7. References

- 1) Brown JV, Lin L, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD000343. DOI: 10.1002/14651858.CD000343.pub4
- 2) Das S, McClintock T, Cormack BE, et al. High protein intake on later outcomes in preterm children: a systematic review and meta-analysis. *Pediatr Res.* 2025; 97:67-80
- 3) Villar J, Giuliani F, Bhutta ZA, et al. International Fetal and Newborn Growth Consortium for the 21(st) Century (INTERGROWTH-21(st)). Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21(st) Project. *Lancet Glob Health.* 2015; 3(11): e681-91
- 4) Greenbury SF, Angelini ED, Ougham K, et al. Birthweight and patterns of postnatal weight gain in very and extremely preterm babies in England and Wales, 2008-19: a cohort study. *Lancet Child Adolesc Health* 2021; 5:719-28
- 5) Greenbury S, Ougham K, Wu J, et al Variation in nutritional practice in neonatal units in England and association with outcomes using agnostic machine learning. *Sci Rep* 2021; 11:7178
- 6) Mills L, Chappell KE, Emsley R, et al Preterm formula, fortified or unfortified human milk for very preterm infants, the PREMFOOD study, a parallel, randomised feasibility trial *Neonatology* 2023 Dec 13:1-11
- 7) Modi N. Management of fluid balance in the very immature neonate. *Arch Dis Child Fetal Neonatal Ed* 2004; 89: F108-11