Consultation Response Form

Document Title: **The use of Donor Human Milk in Neonates**
Closing date: 19/01/2023
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Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
P13, P22, Appendix 6, and general		The document is beneficial for its scope and depth. Thank you. I appreciate the statement about the need for research, the list of uncertainties about the use of DHM (p22), and the constructive suggestions for resolving these by including rationale-driven PICOs (Appendix 6). At points, there appears to be a paradox between strong, unequivocal recommendations and uncertainties in the evidence base. For example, it is counter-intuitive to recommend 'DHM should be offered to all babies born at <32 weeks gestation and/or <1500 grams to establish enteral feeding when MOM is unavailable or insufficient to meet their baby's requirements' and 'DHM is ideally continued until MOM is fully available', while at the same time suggesting PICOs for trials to investigate these interventions. ***Working group response – we have reworded sections of the document to better capture the balance between our recommendations, existing evidence and evidence gaps.***

		I appreciate the transparent statement that recommendations were informed by a 'composite of existing evidence, current practice and healthcare professional and parental feedback' underpinned by an 'ethos of achieving consistency in practice across networks and units'. But for each clinical practice recommendation, in the blue box, could the group go a step further and describe: (i) how existing evidence was weighted in the context of these other drivers; and (ii) the unknowns about conventional scientific measures of efficacy for each intervention that is recommended (i.e., outcomes, effect sizes)? This information would help readers and prospective research funders to understand the extent to which recommendations are based on scientific evidence versus the other relevant drivers. Without this explanation, an unintended consequence of a definitive recommendation in an authoritative BAPM document could be that research to answer the PICOs you have provided becomes more challenging to deliver in the UK. ***Working group response – the working group did not have the expertise or resource to perform an evidence synthesis for all outcomes but we have referenced in more detail the latest WHO recommendations which are informed by expert evidence synthesis. We are also aware of as yet unpublished meta-analysis data which supports the conclusion that DHM as a supplement protects against NEC with moderate certainty.***

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Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
4	Terminology	I was pleased to see that the working group decided to use the term 'mother' throughout and provide a definition of what is meant by the word mother to make it clear who this term includes and excludes. I think that this is a sensible approach and provides both clarity and recognition of the vulnerability of women whose infants may be in need of donor milk who are often in a state of marginalisation due to their infants being in a neonatal intensive care unit. However, I would suggest that the wording of the definition of mother be changed slightly as as it is written the addition of the phrase 'people who have given birth' means that the term 'women' has shifted from a sexed meaning (of adult female people) to a gendered one (meaning anyone who identifies as a woman) so including some male people. Discussion of this shift with so called 'additive language' can be found in a paper I wrote with some others https://www.frontiersin.org/articles/10.3389/fgwh.2022.818856/full - Supplementary file 1 contains similar examples with explanation that you might find helpful. An alternative definition might be 'we use the term … mother to mean those who have gestated and birthed the infant/s for whom donor milk is being considered' or 'we use the term … mother in its sexed sense to mean those who have gestated and birthed the infant/s' You have some usage of the word 'women' in the document and you could consider also providing a definition for women and say 'we use the terms women and mothers in their sexed sense to mean adult female people and female parents respectively with mother referring to those who gestated and birthed the infant/s for whom donor milk is being considered'

		Working group response – thank you for your expert insight. We have decided to continue with our existing wording which aligns with a previous BAPM document on lactation and loss. However BAPM are working towards consistent, sensitive terminology for all publications and you may wish to input into this.

Emma Kolahi, Parent emma_swe@hotmail.co.uk

Page number/ heading / general comments	**Line number/ 'general' for comments**	**Comments** **Please insert each new comment in a new row.**
2	General	Some full stops are in bold & some aren't (I know this is really picky but it's the sort of thing I would have to make consistent in my role outside of the PAG so I thought I would mention it 😊). It might look better if you had the name in bold & then a dash with the job title not in bold, e.g. **Judith Simpson (Chair)** - Neonatologist and Clinical Lead for Milk Bank Scotland
3	5	Explain MOM acronym as I think this is the first time it's used in the document (it's explained further down the document but should be outlined at first use).
3	12	Take out explanation of the MOM acronym (as this should be done on line 6).
3	13	Could use 'neonates who are unwell', rather than 'sick neonates'
3	17	Use a colon after the 'to', before the list starts
4	2	Use a colon after the 'are', before the list starts
4	4 & 6	Take out the full stop at the end of each bullet point
4	11	Take out the comma before 'and'
4	14	Could change 'data are meta-analysed' to 'data is meta-analysed', as it would read better, but not sure if this a direct quote from somewhere (if it is then please ignore me!)
4	27	Could change 'the data are not yet available' to 'the data is not yet available'
6	General	Consider adding 'LBW' & 'NICE' into the list of acronyms at the bottom of the page
6	Outcomes Column	Take spacing out from before & after a / to keep it consistent with the rest of the columns. Space required after the '&', e.g. 'Satisfaction & confidence'
9	29	Could change 'Data from Milk Bank Scotland demonstrate' to 'Data from Milk Bank Scotland demonstrates'
10	10	Could change 'include' to 'included'
11	Secondary Considerations	Could change 'It is clear that other groups of babies are currently receiving, and may benefit from DHM.' to 'It is clear that other groups of babies are currently receiving DHM, & may benefit from this.'
12	5	Change 'aim' to 'aims' & then change 'and increase flexibility' to 'and to increase flexibility'
12	12	Change 'unavailable due local policy' to 'unavailable due to local policy'

12	15	Add a comma after 'of'
13	1.	Could change 'and identify potential gaps in supply' to 'and to identify potential gaps in supply'
15	24	Could change 'where data are not substantiated' to 'where data is not substantiated'
15	26	Add a comma after 'In the UK'
15	27	Take out the comma
15	38	Could take out the comma & add 'and' instead
16	4	Add a comma after 'costs'
16	7	Add a comma after 'provision'
16	10	Add a full stop after 'process'
16	16	Add a comma after 'DHM'
16	18	Add a colon after 'to', before the list starts
16	24	Take spacing out from before & after the / to keep it consistent with the rest of the document
17	3	Change 'cost effective' to 'cost-effective'
20	18	Could change 'in which time' to 'by which time'
20	20	Change 'personalising' to 'personalise'
21	8	Take out 'over'
21	9	Add a comma after 'time'
21	11	Could change 'increase' to 'increased'
21	12	Change 'and previously have' to 'and have previously'
Working group response – thank you for your detailed feedback. We have made the changes you suggest excluding those related to the term data which, we have left as plural although we acknowledge it can be viewed as singular.		

Neena Modi, Professor of Neonatal Medicine, Imperial College London and Chelsea and Westminster NHS FT n.modi@imperial.ac.uk

Page number/ heading / general comments	**Line number/ 'general' for comments**	**Comments** **Please insert each new comment in a new row.**
General comment	1	It is highly plausible that unprocessed own mother's milk (MOM) reduces the risk of necrotising enterocolitis (NEC) as evolutionary science indicates that human milk evolved primarily to serve an antiinfective, not nutritional, purpose. However, milk composition varies between mothers, with many anti-infective and immunological properties uniquely tuned to a specific mother-infant dyad. Additionally, non-nutritional biological components are substantially reduced by pasteurisation and processing undertaken to ensure safety and produce commercial human milk products. Hence, Donated Human Milk (DHM) is not the same as MOM and the benefits of DHM require objective, unbiased evidence. The Framework correctly identifies that there are considerable uncertainties around the benefits of pasteurised DHM in relation to NEC, and possible risks to neurocognitive, and other outcomes.

		A BAPM "Framework" will be viewed as a practice guideline and if this provides recommendations that are insufficiently evidenced-based, risks first, the universal imposition on all patients of practices that might ultimately be shown to be harmful; second, impedes the delivery of randomised controlled trials to resolve these important practice uncertainties; third imposes a cost-pressure unsubstantiated by high-quality evidence on an already under-resourced healthcare system; and fourth, risks bringing disrepute upon the organisation and the profession. **Hence the recommendation in this Framework for extending the non-evidenced use pasteurised DHM is of concern.** ***Working group response – the recommendations have been reframed to ensure greater balance. Notably the recently published WHO evidenced based management recommendations for DHM are similar to this framework and we have provided more information on their methodology and conclusions.***
General comment	2	The lack of evidence of important clinical benefit from use of DHM is indicated by the wide variation in UK practice that is not fully explained by the presence of a milk bank or patient characteristics. This suggests clinical uncertainty about the use of pasteurised DHM (Battersby et al Early Hum Dev 2018; 118:32-36). On average, less than a third of infants born below 32 weeks' gestation in the UK receive any pasteurised human donor milk during their neonatal unit stay (Greenbury et al Identification of variation in nutritional practice in neonatal units in England and association with clinical outcomes using agnostic machine learning. Sci Rep 2021; 11:7178). Uncertainty is bad for patients, raises anxieties for families, and is confusing for staff. My long-standing professional goal is to improve the care of preterm and sick neonates. I am a clinical researcher co-leading the development of an international precision medicine platform trial to test multiple interventions, including DHM, to prevent necrotising enterocolitis (COLLABORATE). Without such research, uncertainties will persist. A patient in one of our focus groups told us "I had NEC as a baby, and 30 years later I had a baby who developed NEC; in 30 years it seems nothing has changed". Without research to resolve uncertainties, nothing will change, and optimal practice will continue to be unidentified. **A Framework that discusses the considerable uncertainty around the place of pasteurised DHM in neonatal care would be welcome. Perhaps the Framework might be rephrased to explain the uncertainties, adding to the excellent summary of research questions, and advising that the best way forward would be for the neonatal community to come together to resolve the uncertainties through high-quality research.** ***Working group response – the document has been revised to achieve a greater balance between consistency in approach (acknowledging the widespread existing use of DHM and the growing demand for it in the context of existing knowledge and remaining evidence gaps) and the need to support future research.***
General comment	3	The preferred feed for all babies is MOM. However, mothers delivering preterm are able on average to supply only about 50% of the volume required. Preterm formula and pasteurised human donor milk are the only options for supplementing any shortfall. Preterm formula has consistent nutrient composition, contains minerals, trace elements and vitamins required by preterm babies, is highly quality-controlled, and is inexpensive (NHS cost: ~£5 per litre). Donor milk products may retain non-nutritive benefits, have variable and often low nutrient density, variable quality-control and are expensive (average cost from UK milk bank: £90-£150/litre; commercial cost up to £2400/litre). Increasing commercialisation of human milk raises ethical concerns. **It is important that the Framework explains the compositional and cost differences, and ethical issues.** ***Working group response – we have made a recommendation that there is increased transparency around the cost of DHM to allow accurate economic evaluation of it as an intervention.***

Page 4/ Introduction	4	The GIRFT recommendation "DHM should be available for high-risk preterm infants in the absence of sufficient MOM", and advocacy "for equity of access across all neonatal units and networks" is not consistent with current UK policy for practice guidance. Thus, the National Institute for Health and Care (NICE) recommendations for equitable access to healthcare products throughout the NHS include a requirement for evidence of patient benefit and cost-effectiveness. At present, neither criterion has been met for DHM. The lack of evidence is why the NICE guideline on Human Milk Banking, on which I was a member, refrained from making clinical recommendations for DHM use. This situation has not changed. **Hence, the BAPM Framework would likely meet with respect if it were rephrased to state, "There should be equity of access to relevant patient groups if DHM is shown to be beneficial; at present conclusive evidence is lacking, hence use is variable and obtaining robust evidence to guide practice is urgently needed".** ***Working group response - the role of GIRFT is to benchmark inequity and advocate for equity of access to something that is considered beneficial by many (clinicians, families, WHO etc). The GIRFT document also underwent extensive stakeholder consultation and revision prior to formal approval and sign off by NHS England, these concerns were not raised. We have recommended in the framework that the NICE guideline on DHM (published in 2010) should be updated.***
Page 4/ Introduction	5	BAPM notes "The Framework is underpinned by the principle that mother's own milk (MOM) feeding is optimal for preterm and/or sick neonates". This is an important statement. However, expression of milk especially over long periods is challenging and can be difficult; many mothers feel pressurised and traumatised by the experience. This reinforces the need to acknowledge evidence suggesting the possibility that promotion of DHM may reduce a mother's m otivation to express. Hard et al (Donor milk does not promote the growth and development of preterm infants as well as maternal milk Acta Pediatrica 2019; 108: 998-1007) discuss the situation in Sweden where extremely preterm infants are fed DHM from a milk bank until a postmenstrual age of approximately 34 weeks if maternal milk production is insufficient, or the mother is unable or chooses not to express milk. Concurrent with the increased use of DHM, the percentage of extremely preterm infants who were exclusively receiving maternal milk at discharge decreased from 55% in 2004 to 16% in 2013. In a reflective discussion they emphasise that a mother's motivation to express milk and breastfeed is influenced by the information that she receives. **Mothers should be presented honestly with a comprehensive summary of the evidence that MOM is superior to DHM, and that strong evidence of benefit of DHM over formula as a supplement to MOM to important functional outcomes is weak.** ***Working group response – we absolutely acknowledge the need parents to be appropriately counselled of the differences between MOM, DHM and IF, the potential risks, benefits and need for further research. We have reinforced this message in the text and added an additional appendix providing an example of the information parents should receive.***
Page 4/ Introduction	6	The sentence "This concept of DHM providing a "bridge" to lactation reinforces the narrative that breast milk feeding is highly valued and has extended the use of DHM within neonatal units, onto postnatal wards and into the wider community" is problematic. There is the problem of condoning "therapeutic creep", a situation in which indications for use of an intervention extend in an ad-hoc and non-evidenced manner. However, of most concern, acknowledged in the introduction, is the possibility of harm from the use of DHM during a particularly crucial period of brain development, namely birth to 34 weeks postmenstrual age. Meta-analyses (Ref 1) and the most recent trial (Colaizy et al, The Milk Trial), clearly show slower growth with DHM, even when nutrient enriched, with no benefit to neurodevelopment. Please also note O'Connor et al (Ref 30) compared development at 18 months' corrected age in very low-birth-weight infants randomised to receive DHM or preterm formula as a supplement to mother's milk. All scores were lower in the DHM group though the differences were not statistically significant. More children

		in the DHM (27.2%) had cognitive composite scores indicative of neuro-impairment (<85) compared with the formula group (16.2%) (Adjusted risk difference 10.6%; 95% CI 1.5% to 19.6%; P = 0.02) and a worse mortality and morbidity index (43% vs 40%). An added conundrum is that in the UK, many clinicians fear that using cow milk-based fortifier to nutrient enrich DHM will increase the risk of NEC; indeed to use a cow milk-based fortifier might negate any potential benefit of avoiding cow-milk based formula. **Thus I would recommend a more nuanced rephrasing of this sentence to acknowledge the uncertainties, and the need to address the possibilities of risks and harms.** ***Working group response – the text in the evidence section has been revised to provide a more nuanced summary, including more detail of the O'Connor findings and a link to the Milk Trial results which do not demonstrate similar non-significant trends towards lower cognitive outcomes in the DHM group. The poorer weight gain in this trial is also highlighted as is the reduction in NEC.***
Page 5/Clinical indications and evidence for donor human milk	7	This section opens with the statement "The main clinical indications for DHM are: 1. To establish enteral feeding in babies at increased risk of necrotising enterocolitis (NEC) when MOM milk is unavailable or insufficient. 2. To support the establishment of lactation in conjunction with breastfeeding support, avoiding the need for supplementation with infant formula". Pasteurisation reduces or destroys many non-nutritive components, but the hope is that DHM retains some beneficial non-nutritive biological properties (which in turn may e.g., reduce NEC). It is also plausible that any reduced risk of NEC by DHM might be mediated indirectly though avoidance of cow milk products rather than any direct non-nutritive biological property. Third, DHM might improve breast feeding, but equally plausibly, might adversely affect motivation to express especially if a mother's is led to believe DHM is equivalent to MOM. However, to-date, there is no convincing high-quality evidence that the use of DHM helps establish enteral feeding or lactation, so this opening statement is unjustified. Available evidence is uncertain; in a systematic review and meta-analysis Williams et al Use of donor human milk and maternal breastfeeding rates J Hum Lact 2016; 32: 212–20) showed no difference in exclusive breastfeeding at hospital discharge in very preterm infants after the introduction of DHM and noted that in certain settings, rates might actually decrease. There is also no conclusive evidence of a difference in NEC and other important functional outcomes between supplementation with formula and supplementation with pasteurised DHM. The most recent Cochrane Library review (Ref 1) identifies only five trials comparing feeding with pasteurised DHM versus formula as a supplement to MOM (Lucas 1984b; Schanler 2005; Corpeleijn 2016; O'Connor 2016; Costa 2018). These showed no significant differences in necrotising enterocolitis (RR 1.56; 95%CI 0.98 to 2.47), all-cause mortality (RR 1.02; 95%CI 0.73 to 1.44), or invasive infection (RR 0.89; 95% CI 0.73 to 1.08). **Thus the opening statements are unjustified and misrepresent the data. The uncertainties in current knowledge should be explained honestly.** ***Working group response – whilst this section opens with globally recognised "clinical" indications for DHM use it then goes on to acknowledge and discuss the limited evidence base, and highlights the need for further research; the text has been revised to add clarity to this.***
Page 5/Clinical indications and evidence	8	The statement "There is extensive clinical experience of using DHM as a strategy to prevent NEC" overstates the strength of the evidence.

for donor human milk		The current Cochrane review and meta-analysis comparing DHM and formula as sole diet or supplement to MOM (Ref 1) identifies nine trials shows a higher risk of necrotising enterocolitis in the formula-fed group (RR 1.87; 95% CI 1.23 to 2.85). However, there are important caveats; first, 4 trials were conducted in the 1980s when the patient population differed substantially from that of today; second, the total number of included infants was only 1675 participants which is an inadequate information size; third, the methodological quality of the studies was poor, and medically managed NEC was included which is an imprecise diagnosis. Fifth, the trials were individually small (ranging from 38 to 362 infants) and repeated meta-analyses of small trials increases the risk of a false positive error (finding a statistically significant difference where none exists). Sixth, and of great importance and relevance is that the meta-analyses identify no significant differences in outcomes that would have provided important corroboratory evidence of a benefit from use of pasteurised DHM, namely all-cause mortality (RR1.10; 95% CI 0.80 to 1.50), invasive infection (RR 0.94; 95% CI 0.79 to 1.12) or days after birth to establish full enteral feeding (MD 0.33; 95% CI -2.57 to 3.23 days). There were also no significant differences in the four trials that evaluated neurodevelopmental outcomes. **Thus a more nuanced opening statement reflective of the uncertainty around the benefits of DHM would seem appropriate.** ***Working group response – the text has been revised accordingly***
Page 5/Clinical indications and evidence for donor human milk	9	The statement "…. but neither does the use of DHM appear to be linked with poorer mid- and long-term outcomes" is misleading. O'Connor et al (Ref 30) compared development at 18 months' corrected age in very low-birth-weight infants randomised to receive DHM or preterm formula, as a supplement to mother's milk. All scores were lower in the DHM group though the differences were not statistically significant. However, more children in the DHM (27.2%) had cognitive composite scores indicative of neuro-impairment (<85) compared with the formula group (16.2%), a difference that was statistically significant (Adjusted risk difference 10.6%; 95% CI 1.5% to 19.6%; P = 0.02) and a worse mortality and morbidity index (43% vs 40%). Colaizy et al (The Milk Trial; abstract only) carried out a randomised trial in extremely preterm infants comparing the effect of nutrient-fortified pasteurised DHM and preterm formula on neurodevelopmental outcomes and found no significant differences. All studies show slower growth with DHM even if nutrient enriched, and no benefits to important functional outcomes (Ref 1). We have unpublished data showing a **lower** chance of survival to 34 weeks postmenstrual age without NEC surgery in babies who received only Own Mother's Milk and pasteurised DHM, compared with babies that received only Own Mother's Milk and preterm formula (Figure). These data are observational and hence should not be used to guide practice but they do indicate clearly that objective high quality randomised controlled data are very urgently needed. **It would be unethical for the Framework to ignore the possibility of harm from use of DHM, in addition to the possibility of benefit or no benefit, and essential that these uncertainties are explained clearly to clinicians and families.** ***Working group response - these are interesting data. Our own experience of using the NNRD dataset to explore feeding outcomes (in a project exploring fortified donor milk versus formula in very preterm infants: retrospective study which is***

		currently in press with Neonatology) was significantly limited by missing data on both milk volume and proportion of each milk type in particular how much MOM relative the supplementation volumes required, it would be interesting to hear how you overcame this limitation when the data is fully in the public domain.
Pages 11/12 Donor human milk use in the UK	10	The relevance of this section to the Framework is unclear. Current or projected use of DHM does not provide any indication of the appropriateness of use. Conversely, variation in clinical practice illustrates uncertainty and the need to resolve this. **The paucity of evidence of important clinical benefit highlighted repeatedly in the Framework is justification not to promote use of HDM but to advocate for rigorous research to identify whether use is beneficial.** ***Working group response – the group felt it was important to describe current practice in the UK to indicate that there is a desire to use DHM and avoid IF despite existing evidence gaps. The text has been modified to acknowledge that limited evidence may be one factor in explaining the variation in practice.***
Page 10/Cultural acceptability of donor human milk	11	Our focus group work with parents indicate clearly that the acceptability of DHM to parents encompasses religious beliefs, cultural views, personal preferences, and the information with which they are provided. We have also shown that parents accept uncertainty as an integral part of many aspects of clinical practice and can be comforted by the knowledge of attempts to resolve uncertainty through a randomised trial (Moss et al More than words: Parent, Patient and Public Involvement perspectives on language used by clinical researchers in neonatal care. Early Hum Dev 2022; 171:105611). Conversely, we identified anxiety and cognitive dissonance among some clinicians in which they recognised the uncertainties that justify a trial but felt unable to participate because of their strongly held views (Lammons et al Incorporating parent, former patient, and clinician perspectives in the design of a national UK double-cluster, randomised controlled trial addressing uncertainties in preterm nutrition. BMJ Paediatr Open 2021; 15;5(1):e001112). **I suggest this section might usefully help clinicians recognise that truly respectful patient care includes honest discussion of uncertainty, a setting aside of personal biases, and a willingness to support high quality randomised controlled trials that aim to resolve uncertainties.** ***Working group response – the group acknowledge that honest and respectful discussions with parents, including discussing uncertainty where it exists underpins good medical practice.***
Page 13/ Recommendations	12	The recommendation "DHM should be offered to all babies born at <32 weeks gestation and/or <1500 grams to establish enteral feeding when MOM is unavailable or insufficient to meet their baby's requirements" is not justified by available evidence, potentially dangerous and illogical. It is dangerous in not acknowledge the possibility of harm from an insufficiently evidenced recommendation. It is illogical because it conflates gestational age and birth weight and ignores the strong association between growth restriction and NEC (i.e. a severely growth restricted baby at or above 32 weeks gestation and weighing more than 1500g is also at risk). **This recommendation would serve babies better if it were restated as follows: "When MOM is unavailable or insufficient to meet their baby's requirements, DHM should be offered to babies born at <32 weeks gestation and other high-risk groups in the context of high-quality randomised controlled trials evaluating important functional outcomes".** ***Working group response – this recommendation has been revised to state "may be" considered and to emphasise the need for appropriate counselling***
Page 13/ Recommendations	13	The recommendation "DHM is ideally continued until MOM is fully available" is dangerous in not acknowledging the possibility of harm and the lack of high-quality supporting evidence. It is also ambiguous in that no definition of "fully available" is provided.

		Harm might arise from prolonged use if pasteurised DHM is nutritionally inadequate. Additionally, the possibility of competing risks is not mentioned in the Framework; thus formula might increase the risk of NEC, but consistent nutritional composition might benefit growth and development. If DHM is shown to be beneficial the appropriate duration of use would depend upon the nature of the benefit. Thus, if use of DHM as a supplement to MOM reduced the risk of severe NEC, it should ideally be continued until the period of major NEC risk had passed. Alternatively, if it were shown to be beneficial to neurodevelopment it would be reasonable to continue as a supplement to insufficient MOM until such time as the baby transitioned to fully suckled feeds at the breast. **Hence, this recommendation would be best removed or rephrased to acknowledge the need for evidence to guide any future recommendation.** ***Working group response – recommendation rephrased, lack of evidence to inform recommendation acknowledged***
Page 13/ Recommendations	14	The point of the recommendation "Access to DHM is valued by healthcare professionals and families, and availability of DHM may have other potential benefits for babies, mothers, donors and wider society" is unclear. Value is sometimes placed inappropriately; for example there are many well-documented instances of patients valuing treatments that are of no benefit or even harmful. DHM may have other benefits, but this is justification for research to identify these benefits, not justification for non-evidenced promotion that may be harmful. **It would be preferable to re-state this recommendation as follows "At present there is substantial variation in the use of and access to DHM; if DHM is shown to beneficial there should be equity of access to all groups of babies that might benefit".** ***Working group response - the group felt that it was important to acknowledge that introducing DHM is a complex intervention, potentially impactful on a number of differing outcomes – as highlighted in Figure 1 in the document.***
Page 13/ Recommendations	15	The recommendation "All neonatal units and networks should work collaboratively to produce local guidelines to ensure that practice is consistent and addresses what matters to families" is dangerous because it risks imposing on all babies, practices that do not have a strong evidence base and may ultimately be shown to be harmful. This mistake, namely the implementation of non-evidenced based guidelines has been made many times previously in neonatal medicine. A key example is the routine use of 100% oxygen during resuscitation; clinical trials were held back for many decades because the practice had entered into routine care. When clinicians set aside their biases and supported randomised controlled trials the practice was found to be harmful. However, this was not until many thousands of babies had suffered adverse consequences. For this reason, where there is uncertainty, the recommendation that best benefits patients is to put the uncertainty to the test of randomisation. **Therefore, this recommendation would be better restated as follows: "All neonatal units and networks should work collaboratively to explain existing uncertainties to families and support high quality research to produce evidence to guide best practice in relation to DHM use".** ***Working group response – the group has highlighted existing evidence and also existing uncertainties and recommends that the neonatal community should fully support further research where equipoise exists.***
Page 14/ Milk banking infrastructure	16	The Framework states "What is unclear from the GIRFT findings is whether DHM is unavailable due local policy, a perceived lack of availability due to the absence of a local HMB/hub/depot, or an actual shortfall in DHM supply".

in the UK		The wide variation in UK practice relating to DHM is not explained by the presence of a milk bank or patient characteristics (Battersby et al Early Hum Dev 2018; 118:32-36). **This suggests that clinical uncertainty about the benefits of pasteurised DHM is an important contributor to variation in use, a point that should be acknowledged in the Framework.** ***Working group response – text expanded to include this***
Page 19/ Commercialisation of human milk	17	The section on the "Commercialisation of human milk" might usefully highlight the analogies between the situation vis a vis donor/provider human milk/human milk products today, and that in the 1980s in relation to the promotion of infant formula. Aggressive marketing coupled with claims about the benefits of infant formula adversely affected breast feeding. We are witnessing an equivalent situation today in relation to DHM/products. If these are promoted by clinical communities and professional bodies despite the lack of a secure evidence-base, commercial companies will do likewise. There is a real risk that mothers will then choose these products to the detriment of breast-feeding and incur increased costs. **This section could be usefully reframed to expand on why human milk products should be regarded as a unique category that requires standards separate from those of foods, why companies should show evidence of functional benefit, and why regulators should require such evidence. However, clearly the same standards should hold for pasteurised DHM from Human Milk Banks.** ***Working group response – we feel we have addressed these issues in the document and we have also added a little more in relation to the recent high lead content concerns.***
Pages 27-28	18	The working group is imbalanced in including a predominance of individuals who have a personal professional and/or financial bias towards promoting pasteurised DHM, and a lack of individuals able to provide equipoise; **this opens the Framework to serious criticism** ***Working group response – there is a robust process behind the formation of every BAPM working group. Members are invited to apply to join the group and the aim is to create a group that has the appropriate expertise but also diversity in terms of multidisciplinary roles, geographical location across the devolved nations and trainee engagement. This process was followed and in addition any potential conflicts of interest are clearly identified.***
Appendix 6	19	The Framework includes research questions in PICO format, but these are placed in an appendix. It would be of help especially to non-research active readers if these uncertainties and the urgent need to resolve them were explained clearly within the main body of the Framework. ***Working group response – we did consider having these within the text but decided that they were more appropriate as an appendix. However we have re-ordered the text and pulled the section on the ongoing uncertainties to earlier in the document to give greater emphasis.***
Page 37/Appendix 6/ First row	20	The statement "The current Cochrane meta-analysis1 shows that when DHM is used as a supplement to make up any shortfall in MOM the reduction in NEC is of borderline significance" is incorrect. When DHM is used as a supplement to make up a shortfall in MOM there is no significant difference in NEC; the Relative Risk is 1.56; 95%CI 0.98 to 2.47. Please note this research question will be addressed in the COLLABORATE platform ***Working group response – we are aware of unpublished data of an updated meta-analysis which shows there is no difference and the evidence of benefit remains of moderate certainty.***

Page 37/Appendix 6/ First row	21	It is stated "there is opposition (to comparing DHM with preterm formula as a supplement to make up any shortfall in MOM) from both PPI and many clinicians". We have conducted a national survey of clinicians and focus groups with parents in the UK and across Europe, supported by Bliss and the European Foundation for the Care of Newborn Infants. When the evidence and rationale are presented only a small minority of clinicians indicated they would not take part in such a trial, and no parents. This statement is therefore not an accurate reflection of objective evidence of clinician and parent views. ***Working group response – this is interesting and not reflective of many of the group's experience.***
Page 37/Appendix 6/ Second row	22	"Observational data suggest that availability of DHM creates a more positive culture towards breastmilk in general but no adequately powered trials exist"; in actuality it is anecdotal data that suggest this. Observational data show considerable uncertainty in either direction. Available evidence is uncertain; In a systematic review and meta-analysis Williams et al Use of donor human milk and maternal breastfeeding rates J Hum Lact 2016; 32: 212–20) showed no difference in exclusive breastfeeding at hospital discharge in very preterm infants and noted that in certain settings, rates might actually decrease after the introduction of DHM. ***Working group response – 2 members of the working group were co-authors on this publication and are aware of the finding (based on limited data) of no impact on breast feeding rates at discharge, hence the importance of further study.***
Page 37/Appendix 6/Third row	23	The comment is made that the high cost of an exclusive human milk diet could be justified if one less case of NEC occurred for every 20-30 babies. We showed in a two-year whole population study that 50% of all cases of severe NEC (leading to surgery and/or death) received an exclusive human milk diet prior to disease onset (Battersby et al Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. Lancet Gastroenterol Hepatol 2017; 2: 43-51). We also showed in this study that for babies who received no bovine-origin products compared with any bovineorigin products within 14 days of birth, the number needed to treat (i.e. with an exclusive human milk diet) to prevent one case of severe NEC was 154, 95%CI 99 to 345). Thus it is important that the potential benefits of an exclusive human milk diet are examined objectively in high quality randomised controlled trials. This is one aim of the current COLLABORATE platform. ***Working group response – we agree that a significant proportion of severe NEC occurs in babies of have only received human milk, emphasising the need for further mechanistic understanding of NEC, gut function and the role human milk plays. We look forward to hearing more about the COLLABORATE proposals.***
Page 37/Appendix 6/Fourth row	24	"In preterm infants <32 weeks or <1500 grams receiving DHM to make up any shortfall in MOM I. Does the routine use of a BMF C. Compared to only using a BMF if growth is faltering O. Result in better 2-year outcomes?" This research question will be addressed in the COLLABORATE platform ***Working group response – excellent.***

Karen Read, Professional Lead for Neonatal, Baby Friendly Initiative karenr@unicef.org.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
7	outcomes	Under babies specifies less disease (NEC, BPD etc) however in the previous section, illnesses other than NEC seem to have little evidence connected with DBM and a reduction.
		Will there be an executive summary?
		Working group response - yes
	recommendations	Some of the recommendations are comments, could this be clarified with the heading of the recommendation sections? Recommendations and considerations
		Working group response - recommendations revised so less necessary

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Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Page number 3		It is striking that 8 out of the 15 members of the Working Group have personal, professional and potentially financial interests in promoting the use of banked human milk. This undermines the objectivity of the recommendations contained in the document. ***Working group response – there is a robust process behind the formation of every BAPM working group. Members are invited to apply to join the group and the aim is to create a group that has the appropriate expertise but also diversity in terms of multidisciplinary roles, geographical location across the devolved nations and trainee engagement. This process was followed and in addition any potential conflicts of interest are clearly identified.***
Page 4		*It aligns with the Neonatology Getting It Right First Time (GIRFT) Report (Neonatology GIRFT national report > – Getting It Right First Time – GIRFT) recommendation that DHM should be available for high risk preterm infants in the absence of sufficient MOM, and advocates for equity of access across all neonatal units and networks.* Comment: The role of GIRFT is to highlight variation in practice. However, they do not conduct an evidence synthesis, literature review or economic analysis to back any recommendations. Therefore, using this as evidence to support the BAPM Framework is not justified. ***Working group response; see answer to GIRFT reference above.***

Page 5		Although available evidence is limited, a consistent finding when compared to IF is that DHM reduces the incidence of preterm NEC. This is most striking when the data are meta-analysed1 and/or systematically reviewed2. No evidence of benefit from the use of DHM on other preterm morbidities, longer term outcomes or mortality has been convincingly described, but neither does the use of DHM appear to be linked with poorer mid- and long-term outcomes Comment: Absence of evidence is not evidence of absence. This is also not an accurate conclusion of the meta-analysis. Given the limited evidence of the benefits of DHM the emphasis of the framework on promoting DHM risks future research being compromised by reinforcing non-evidence-based practice and consequent lack of equipoise resulting from guidance issued by professional bodies such as BAPM that many will follow. ***Working group response - our conclusions align with recently published WHO advice and aim to promote a consistent approach across neonatal units / networks. The need for further research to address evidence gaps is clearly highlighted and has been strengthened in light of helpful consultation feedback.***
Page 8		What do we learn from recipient families and staff? Comment: It would be good to see comments from a range of professionals and lay persons. Has this been actively sought? ***Working group response – comments have been actively sought from families and staff, samples of which are included. We did try to obtain negative as well as positive comments but none were forthcoming***
Page 13		D_H_M_ _s_h_o_u_l_d_ _b_e_ _o_f_f_e_r_e_d_ _t_o_ _a_l_l_ _b_a_b_i_e_s_ _b_o_r_n_ _a_t_ _<_3_2_ _w_e_e_k_s_ _g_e_s_t_a_t_i_o_n_ _a_n_d_/_o_r_ _<_1_5_0_0_ _g_r_a_m_s_ _t_o_ _e_s_t_a_b_l_i_s_h_ _e_n_t_e_r_a_l_ _f_e_e_d_i_n_g_ _w_h_e_n_ _M_O_M_ _i_s_ _u_n_a_v_a_i_l_a_b_l_e_ _o_r_ _i_n_s_u_f_f_i_c_i_e_n_t_ _t_o_ _m_e_e_t_ _t_h_e_i_r_ _b_a_b_y_’s_ _r_e_q_u_i_r_e_m_e_n_t_s_._ _ Comment: ‘Should’, should only be used when the evidence is convincing. ‘Consider using’ would be more appropriate and in keeping with uncertainty around its use. The possibility of harm from feeding a low nutrient product during a period of rapid brain growth (O’Connor et al showed worse neurodevelopment with DHM) has to be considered. Unless safety concerns are ruled out strong recommendations based on weak recommendations may result in harm to babies. ***Working group response – wording revised to may be considered and need for counselling reinforced***

Juliette Ward, Tommy’s Midwife JWard@tommys.org

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
8	general	The early emphasis on the voices of recipient families is vital as is an understanding that there is no one homogeneous group pf "recipient parents" – as such the dynamic between parents and staff will need to be based on an understanding of the unique needs of each family. Listening to the voices of parents needs to be seen as an on-going and evolving process.
13	general	This is helpfully very clear.
15	general	Again – helpfully very clear. All recommendations being in the same format offers clarity and consistency and makes the information more easily accessible.
18	general	As above (pgs 13 & 15)
21	general	As above (pgs 13 &15)
		Working group response – thank you for taking the time to reply

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
10	General	It is disappointing that you did not include any reference to the largest comparative ethnographic study of donor human milk culture conducted across the UK? This book specifically discusses the acceptability of donor human milk across the UK to a number of families, and is available by open access since August 2022. I feel it could and should referenced here. Cassidy T. M., Dykes F., with Mahon B. (2019). *Banking on Milk: An ethnography of human milk exchange relations*. London: Routledge. ***Working group response – thank you for highlighting this omission, book now referenced***
19	Commercialisation of human milk beginning	Because the report is about donor milk, I feel it is important to point out that donor human milk services in England predate the NHS and so were originally funded through charity funds (another point made in *Banking on Milk*). That said, today all of the not-for-profit services in the UK, but one, are within the NHS. However, there are different models for funding these services across the UK. The model in Scotland supports equity of access to service while at the same time having the cost be distributed across health trusts. Allowing these vital services to not be fully funded by the health system has contributed to a culture of commercialisation regarding human milk in the UK. Currently the system in some parts of the UK has the NHS supporting the commercialisation of human milk, and therefore opening this market to potential exploitation.

		This is especially a consideration when we think about mothers in the community, some of whom may have legitimate medical need for such a service and should also be supported within an NHS frame. When this doesn't happen commercial companies recognise a gap in a potential market. There may also be other families unable to provide mother's own milk to their infant(s) but who do not have the same medical need (perhaps considering same sex couples) and the NHS would need to consider on a case by case basis if these needs should be supported. Those families who are not supported by the NHS may turn to commercial or underground markets to obtain human milk, and these may even involve human milk being shipped from other countries, involving the potential for international exploitation. ***Working group response – thank you for these valid points.***