EtD 35. In preterm infants receiving enteral feeds does enteral additional protein intake improve growth, clinical outcomes or neurodevelopment, or reduce NEC, gastrointestinal complications or less metabolic bone disease?

POPULATION:	Preterm infants receiving enteral feeds
INTERVENTION:	Additional enteral protein supplementation
COMPARISON:	No additional protein supplementation
MAIN OUTCOMES:	**Critical outcomes** Mortality Neurodevelopmental impairment Faltering growth/body composition Necrotising enterocolitis **Important but not critical** Adverse effects (gastrointestinal complications) Time to full enteral feeds Duration of initial hospital stay Fully breastfed or breastmilk feeding at hospital discharge Sepsis: proven or suspected Bronchopulmonary dysplasia Retinopathy of prematurity Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Less important for decision making** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation: population perspective
BACKGROUND:	Protein is a critical macronutrient for preterm infants, playing a central role in brain and other organ development, and tissue growth. Due to their rapid growth needs and limited body stores, preterm infants have higher protein requirements than term infants. These high protein requirements are not met by expressed breastmilk alone, even at very high volumes. Achieving adequate protein intake through enteral feeds is essential to support optimal growth, neurodevelopment, and overall health outcomes in this vulnerable population. Additional protein intake may promote better weight gain, lean body mass and enhance neurodevelopmental outcomes. However, the benefits of additional protein must be weighed against potential risks, including feeding intolerance, gastrointestinal complications, and neurotoxicity due to protein overload. Excessive protein intake may contribute to metabolic acidosis and elevated blood amino acids concentrations, particularly in infants with immature renal function. Additional protein may also increase the risk of necrotising enterocolitis and other gastrointestinal complications and may delay reaching full enteral feeds. Defining the optimal protein intake for preterm infants to ensure improved growth, neurodevelopment and clinical outcomes while minimising the

	risk of adverse outcomes remains a key consideration in neonatal nutritional management. This question relates to protein supplementation that is in addition to, or instead of commercial breastmilk fortifier.
CONFLICT OF INTERESTS:	The following Das *et al* systematic review co-authors are on the Guideline Development Group: Luling Lin and Frank Bloomfield and Barbara Cormack. The following Amissah *et al* systematic review co-author wrote this Evidence to Decision document: Julie Brown

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Evidence based on two Cochrane reviews [1] and [2] and another systematic review [3]. **NB This question relates to the optimal amount of enteral protein supplementation from or in addition to breastmilk fortifier or preterm formula** **Currently available fortifiers add either 1.3 or 1.4 g/kg/day of protein to breastmilk to make total protein intakes of:** 160 mL/kg/day fortified expressed breastmilk provides 4.0 to 4.3 g/kg/day 180 mL/kg/day fortified expressed breastmilk provides 4.4 to 4.9 g/kg/day 160 mL/kg/day preterm formula provides 4.3 to 4.6 g/kg/day 180 mL/kg/day preterm formula provides 4.9 to 5.2 g/kg/day **Studies reporting the optimal amount of protein supplementation from or in addition to breastmilk fortifier only** **No faltering growth/body composition**: RCT: There was no significant difference between higher and lower protein for weight gain (SMD 0.27 SD higher; 0.1 lower to 0.64 higher). Meta-regression revealed a significant linear relationship between protein intake and weight gain (5.73 g/kg/day weight gain for each gram of protein/kg/day, p= 0.001). After adjusting for the energy intake in the included studies, this effect size increased to 8.78 g/kg/day for each additional gram per kg per day of protein intake [Critical]. **No faltering growth/body composition**: RCT: There was a significant increase for length gain for higher compared with lower protein (SMD 0.5 SD higher; 0.08 higher to 0.92 higher). The relationship between protein intake and length gain became significant once energy intake was adjusted for, with each gram per kg per day of protein intake associated with a 0.78 mm per week increase in length. (p≤0.001) [Critical]. **No faltering growth/body composition**: RCT: There was no significant difference between higher and lower protein for head circumference gain (SMD 0.06 SD higher; 0.46 lower to 0.59 higher) [Critical].	**Population information for included evidence** Systematic review of the effects of protein intake from fortified human milk in very preterm infants <32 weeks' gestation [4]. **Higher protein** was defined as 3.2 to 4.5 g/kg/day in four studies and 3.9–to 4.7 g/kg/day in six studies. **Lower protein** was defined as 2.9–to 4.0 g/kg/day and 3.2–4.2 g/kg/day. Cochrane systematic review [2]: preterm infants <37 completed weeks. The protein added from breastmilk fortifier was classified as: **Low <1 g protein** added to 100 mL EBM **Moderate ≥1g to <1.4 g protein** added to 100 mL EBM **High ≥ 1.4 g protein** added to 100 mL EBM Trials that compared two protein concentrations that fell within the same category as above were excluded. Systematic review [3]: preterm infants <37

	Studies reporting the optimal amount of protein supplementation from or in addition to breastmilk fortifier or preterm formula **Mortality**: RCT: High vs. moderate protein: No deaths in either the high or moderate protein groups [Critical]. **Mortality**: RCT: Moderate vs. low protein: No significant effect for reduced risk of mortality with moderate protein intake (19 fewer per 1,000; 35 fewer to 152 more) [Critical]. **Neurodevelopmental impairment**: RCT: No significant reduction in cerebral palsy for high vs. low protein (8 fewer per 1,000**;** 48 fewer to 212 more) [Critical]. **No faltering growth/body composition**: RCT: Very large increase in weight gain for protein supplementation (MD 3.8 g/kg/day higher; 2.9 higher to 4.7 higher). Small increase in length gain (MD 0.12 cm/week higher; 0.07 higher to 0.17 higher) and in head growth (MD 0.06 cm/week higher; 0.01 higher to 0.12 higher) [Critical]. **No faltering growth/body composition**: RCT: *High versus moderate protein supplementation*: Small increase in weight gain for high protein compared with moderate protein supplementation (MD 0.66 g/kg/day higher; 0.51 higher to 0.82 higher). No significant effect on length gain (MD 0.01 cm/week higher; 0.01 lower to 0.03 higher) or increase in head circumference (MD 0 cm/week; 0.01 lower to 0.02 higher). However, in the subgroup of trials that compared isocaloric fortifiers, there was a higher rate of length gain in infants fed a high versus moderate protein fortifier (MD 0.05 cm/week, 95% CI 0.01 to 0.09; studies = 4; N= 418), whereas there was no difference in length gain in the one trial that compared fortifiers that were non-isocaloric (MD 0.00 cm/week, 95% CI −0.02 to 0.02; N= 129). There were no subgroup differences by energy content for the outcomes of weight gain or head circumference gain [Critical]. **No faltering growth/body composition**: RCT: *Moderate versus low protein supplementation*: Very large increase in weight gain for moderate protein compared with low protein supplementation (MD 2.08 g/kg/day higher; 0.38 higher to 3.77 higher). Little or no increase in length gain (MD 0.09 cm/week higher; 0.05 higher to 0.14 higher) or increase in head circumference (MD 0.13 cm/week higher; 0 to 0.26 higher) [Critical]. **No faltering growth/body composition**: RCT: No significant effect on length in infancy for *high vs. low protein* (MD 0.18 cm higher; 0.61 lower to 0.97 higher) or length/height during the toddler period (MD 0.22 cm higher; 0.35 lower to 0.79 higher) [Critical]. **Necrotising enterocolitis**: RCT: No significant reduction in NEC with *high versus moderate* protein supplementation (9 fewer per 1,000; 30 fewer to 52 more). No significant effect on NEC with *low* protein supplementation compared with *moderate* supplementation (1 fewer per 1,000; 17 fewer to 255 more) [Critical]. **Duration of initial hospital stay**: RCT: *Moderate vs. low protein supplementation*: No significant reduction in duration of hospital stay for moderate protein supplementation (MD 3 days lower; 7.13 lower to 1.13 higher) [Important]. **Sepsis**: RCT: *Moderate versus low protein* concentration: No significant reduction in risk of	completed weeks. **low <3.5 g/kg/d** total protein intake **High ≥3.5 g/kg/d** total protein intake (2) Cochrane systematic review. included 4 studies of infants <32 weeks' gestation, one <33 weeks' and one up to and including 36 weeks' gestation.

	sepsis for moderate protein supplementation (19 fewer per 1,000; 35 fewer to 152 more) [Important]. **Desirable effects for Māori** No additional evidence available.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no additional protein supplementation	Risk difference with additional protein supplementation
Mortality: RCT: High vs. moderate protein	101 (5 RCTs)	⨁⨁⨁◯ Moderate[a]	-	None of the trials reported any deaths in either group	
Mortality: RCT: Moderate vs. low protein	112 (1 RCT)	⨁◯◯◯ Very low[b,c]	**RR 0.48** (0.05 to 5.17)	Study population	
				36 per 1,000	**19 fewer per 1,000** (35 fewer to 152 more)
Neurodevelopmental impairment: RCT: High vs. low protein assessed with: Survival without neurodisability at or beyond 12 months' corrected age [measure not specified in review]	400 (1 RCT)	⨁◯◯◯ Very low[c,d,h]	**RR 0.94** (0.85 to 1.05)	Study population	
				927 per 1,000	**56 fewer per 1,000** (139 fewer to 46 more)
Neurodevelopmental impairment: RCT: High vs. low protein assessed with: Cerebral palsy during toddler period [measure not specified in review]	926 (2 RCTs)	⨁◯◯◯ Very low[c,e,f]	**RR 0.85** (0.15 to 4.79)	Study population	
				56 per 1,000	**8 fewer per 1,000** (48 fewer to 212 more)
Faltering growth/body composition: RCT: Protein source from human milk fortification only assessed with: Weight gain (g/kg/day)	530 (8 RCTs)	⨁◯◯◯ Very low[c,g,h]	-	The mean faltering growth/body composition: RCT: Protein source from human milk fortification only was **17.65 g/kg/day**	SMD **0.27 SD higher** (0.1 lower to 0.64 higher)
Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	101 (5 RCTs)	⨁⨁◯◯ Low[c,g]	-	The mean faltering growth/body composition: RCT was **14.68 g/kg/day**	MD **3.82 higher** (2.94 higher to 4.7 higher)
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Weight gain (g/kg/day)	606 (6 RCTs)	⨁⨁⨁⨁ High	-	The mean faltering growth/body composition: RCT: High vs. moderate protein was **16.56 g/kg/day**	MD **0.66 higher** (0.51 higher to 0.82 higher)
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Weight gain (g/kg/day)	176 (2 RCTs)	⨁◯◯◯ Very low[c,i]	-	The mean faltering growth/body composition: RCT: Moderate vs. low protein was **13.79 g/kg/day**	MD **2.08 higher** (0.38 higher to 3.77 higher)
Faltering growth/body composition: RCT: Protein source from human milk fortification only assessed with: Length gain (mm/week)	174 (3 RCTs)	⨁⨁⨁⨁ High	-	The mean faltering growth/body composition: RCT: Protein source from human milk fortification only was **1.00 mm/week**	SMD **0.5 SD higher** (0.08 higher to 0.92 higher)

Faltering growth/body composition: RCT assessed with: Length gain (cm/week)	68 (4 RCTs)	⨁◯◯◯ Very low[a,c,i]	-	The mean faltering growth/body composition: RCT was **0.75 cm/week**	MD **0.12 higher** (0.07 higher to 0.17 higher)
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Length gain (cm/week)	547 (5 RCTs)	⨁⨁⨁⨁ High	-	The mean faltering growth/body composition: RCT: High vs. moderate protein was **1.11 cm/week**	MD **0.01 higher** (0.01 lower to 0.03 higher)
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Length gain (cm/week)	217 (3 RCTs)	⨁⨁◯◯ Low[c,f]	-	The mean faltering growth/body composition: RCT: Moderate vs. low protein was **0.8 cm/week**	MD **0.09 higher** (0.05 higher to 0.14 higher)
Faltering growth/body composition: RCT: High vs. low protein assessed with: Length in infancy (cm)	617 (2 RCTs)	⨁◯◯◯ Very low[c,i]	-	The mean faltering growth/body composition: RCT: High vs. low protein was **69.31 cm**	MD **0.18 higher** (0.61 lower to 0.97 higher)
Faltering growth/body composition: RCT: High vs. low protein assessed with: Length/height during toddler period (cm)	1017 (3 RCTs)	⨁◯◯◯ Very low[c,i]	-	The mean faltering growth/body composition: RCT: High vs. low protein was **79.73 cm**	MD **0.22 higher** (0.35 lower to 0.79 higher)
Faltering growth/body composition: RCT: Protein source from human milk fortification only assessed with: Head circumference (mm/week)	174 (3 RCTs)	⨁⨁◯◯ Low[h,i]	-	The mean faltering growth/body composition: RCT: Protein source from human milk fortification only was **0.93 mm/week** SD	SMD **0.06 SD higher** (0.46 lower to 0.59 higher)
Faltering growth/body composition: RCT assessed with: Head growth (cm/week)	68 (4 RCTs)	⨁◯◯◯ Very low[a,c,g]	-	The mean faltering growth/body composition: RCT was **0.79 cm/week**	MD **0.06 higher** (0.01 higher to 0.12 higher)
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Head circumference gain (cm/week)	549 (5 RCTs)	⨁⨁⨁⨁ High	-	The mean faltering growth/body composition: RCT: High vs. moderate protein was **0.84 cm/week**	MD **0** (0.01 lower to 0.02 higher)
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Head circumference growth (cm/week)	217 (3 RCTs)	⨁◯◯◯ Very low[c,i]	-	The mean faltering growth/body composition: RCT: Moderate vs. low protein was **0.76 cm/week**	MD **0.13 higher** (0 to 0.26 higher)
Necrotising enterocolitis: RCT	76 (1 RCT)	⨁◯◯◯ Very low[a,b,d]	**RR 1.11** (0.07 to 17.12)	Study population	
				25 per 1,000	**3 more per 1,000** (23 fewer to 403 more)
Necrotising enterocolitis: RCT: High vs. moderate protein	326 (4 RCTs)	⨁⨁⨁◯ Moderate[h]	**RR 0.78** (0.27 to 2.27)	Study population	
				41 per 1,000	**9 fewer per 1,000** (30 fewer to 52 more)
Necrotising enterocolitis: RCT: Moderate vs. low protein	112 (1 RCT)	⨁◯◯◯ Very low[a,d,j]	**RR 0.96** (0.06 to 15.05)	Study population	
				18 per 1,000	**1 fewer per 1,000**

					(17 fewer to 255 more)
Adverse effects (gastrointestinal complications) - not measured	-	-	-	-	-
Time to full enteral feeds: RCT assessed with: Feeding intolerance	17 (1 RCT)	⨁◯◯◯ Very low[a,j]	**RR 2.70** (0.13 to 58.24)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Time to full enteral feeds RCT: High vs. moderate protein assessed with: Days	162 (2 RCTs)	⨁⨁⨁◯ Moderate[h]	-	The mean time to full enteral feeds RCT: High vs. moderate protein was **12.5 days**	MD **0.26 higher** (1.78 lower to 2.31 higher)
Duration of initial hospital stay: RCT assessed with: Days	20 (1 RCT)	⨁◯◯◯ Very low[b,c,d]	-	The mean duration of initial hospital stay: RCT was **48.7 days**	MD **18.5 higher** (4.39 higher to 32.61 higher)
Duration of initial hospital stay: RCT: High vs. moderate protein assessed with: Days	92 (1 RCT)	⨁⨁◯◯ Low[b,d]	-	The mean duration of initial hospital stay: RCT: High vs. moderate protein was **73 days**	MD **4 higher** (3.71 lower to 11.71 higher)
Duration of initial hospital stay: RCT: Moderate vs. low protein assessed with: Days	41 (1 RCT)	⨁⨁◯◯ Low[d,h]	-	The mean duration of initial hospital stay: RCT: Moderate vs. low protein was **17 days**	MD **3 lower** (7.13 lower to 1.13 higher)
Sepsis: proven or suspected: RCT: Moderate vs. low protein	112 (1 RCT)	⨁◯◯◯ Very low[b,d]	**RR 0.48** (0.05 to 5.17)	Study population	
				36 per 1,000	**19 fewer per 1,000** (35 fewer to 152 more)
Sepsis: proven or suspected: RCT: High vs. moderate protein	326 (4 RCTs)	⨁⨁⨁◯ Moderate[h]	**RR 1.18** (0.51 to 2.73)	Study population	
				53 per 1,000	**9 more per 1,000** (26 fewer to 91 more)
Bronchopulmonary dysplasia - not measured	-	-	-	-	-
Retinopathy of prematurity - not measured	-	-	-	-	-
Anaemia of prematurity - not measured	-	-	-	-	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-

a) a. Downgraded one level for imprecision due to low event numbers or participant numbers
b. Downgraded two levels for very wide confidence intervals crossing the line of no effect suggesting imprecision with benefit and harm

a)
a. Downgraded one level for risk of bias concerns
b. Downgraded one level for indirectness as only reported in a single study
c. Downgraded one level for inconsistency following visual inspection of forest plot

d. Downgraded one level for imprecision due to wide confidence intervals
e. Downgraded one level for inconsistency as I2 = 60-80%
f. Downgraded one level for imprecision due to confidence intervals crossing the line of no effect
g. Downgraded two levels for inconsistency as I2 >80%
h. Downgraded three levels for extremely wide confidence intervals crossing the line of no effect indicating significant benefit and harm

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Studies reporting the optimal amount of protein supplementation from or in addition to breastmilk fortifier or preterm formula** **Neurodevelopmental impairment:** RCT: No significant effect on survival without neurodisability at or beyond 12 months' corrected age for high vs. low protein (56 fewer per 1,000; 139 fewer to 46 more) [Critical] **Necrotising enterocolitis:** RCT: No significant increase in NEC with protein supplementation (3 more per 1,000; 23 fewer to 403 more) [Critical]. **Full enteral feeds**: RCT: No effect on time to full enteral feeds (days) between protein and no protein supplementation (0 fewer per 1,000; 0 fewer to 0 fewer) [Important]. **Full enteral feeds:** RCT: High versus moderate protein supplementation: No significant effect on time to full enteral feeds (days) (MD 0.26 days higher; 1.78 lower to 2.31 higher) [Important]. **Duration of initial hospital stay**: RCT: Very large effect for increased duration of hospital stay for protein supplementation (MD 18.5 days higher; 4.39 higher to 32.61 higher) [Important]. **Duration of initial hospital stay**: RCT: High vs. moderate protein supplementation: No significant increase in duration of hospital stay for high protein supplementation (MD 4 days higher; 3.71 lower to 11.71 higher) [Important]. **Sepsis**: RCT: High versus moderate protein supplementation: No significant increase in risk of sepsis with high protein supplementation (9 more per 1,000; 26 fewer to 91 more) [Important] **Undesirable effects for Māori** No additional evidence available	Effects described are on weight gain, (not necessarily on avoiding faltering growth). The disproportionate effect on weight gain but much less effect on length or head circumference gain may be undesirable.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low	High to very low evidence overall	

○ Low ○ Moderate ○ High ○ No included studies	**Certainty of evidence for Māori** No additional evidence available.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality: RCT: High vs. moderate protein	CRITICAL	⨁⨁◯◯ Low
Mortality: RCT: Moderate vs. low protein	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: High vs. low protein assessed with: Survival without neurodisability at or beyond 12 months' corrected age [measure not specified in review]	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: High vs. low protein assessed with: Cerebral palsy during toddler period [measure not specified in review]	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: Protein source from breastmilk fortification only assessed with: Weight gain (g/kg/day)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Weight gain (g/kg/day)	CRITICAL	⨁⨁⨁⨁ High
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Weight gain (g/kg/day)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: Protein source from breastmilk fortification only assessed with: Length gain (cm/week)	CRITICAL	⨁⨁⨁⨁ High
Faltering growth/body composition: RCT assessed with: Length gain (cm/week)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Length gain (cm/week)	CRITICAL	⨁⨁⨁⨁ High
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Length gain (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: High vs. low protein assessed with: Length in infancy (cm)	CRITICAL	⨁◯◯◯ Very low

Faltering growth/body composition: RCT: High vs. low protein assessed with: Length/height during toddler period (cm)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: Protein source from breastmilk fortification only assessed with: Head circumference (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT assessed with: Head growth (cm/week)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: High vs. moderate protein assessed with: Head circumference gain (cm/week)	CRITICAL	⨁⨁⨁⨁ High
Faltering growth/body composition: RCT: Moderate vs. low protein assessed with: Head circumference growth (cm/week)	CRITICAL	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT	CRITICAL	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT: High vs. moderate protein	CRITICAL	⨁⨁⨁◯ Moderate
Necrotising enterocolitis: RCT: Moderate vs. low protein	CRITICAL	⨁◯◯◯ Very low
Adverse effects (gastrointestinal complications) - not measured	IMPORTANT	-
Time to full enteral feeds: RCT assessed with: Feeding intolerance	IMPORTANT	⨁◯◯◯ Very low
Time to full enteral feeds RCT: High vs. moderate protein assessed with: Days	IMPORTANT	⨁⨁⨁◯ Moderate
Duration of initial hospital stay: RCT assessed with: Days	IMPORTANT	⨁◯◯◯ Very low
Duration of initial hospital stay: RCT: High vs. moderate protein assessed with: Days	IMPORTANT	⨁⨁◯◯ Low[b,e]
Duration of initial hospital stay: RCT: Moderate vs. low protein assessed with: Days	IMPORTANT	⨁⨁◯◯ Low
Sepsis: proven or suspected: RCT: Moderate vs. low protein	IMPORTANT	⨁◯◯◯ Very low
Sepsis: proven or suspected: RCT: High vs. moderate protein	IMPORTANT	⨁⨁⨁◯ Moderate

Bronchopulmonary dysplasia - not measured	IMPORTANT	-
Retinopathy of prematurity - not measured	IMPORTANT	-
Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds - not measured	NOT IMPORTANT	-

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Possibly important uncertainty or variability **Values for Māori** No additional evidence available.	

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention	**Studies reporting the optimal amount of protein supplementation from or in addition to breastmilk fortifier only** **Higher protein compared with lower protein - high certainty evidence** Increase in length gain and increase in length gain when adjusted for energy intake **Higher protein compared with lower protein - low certainty evidence** Uncertain effect on head circumference **Higher protein compared with lower protein - very low certainty evidence**	Meta-regression [4] suggested most preterm infants may require 4.0–4.5 g/kg/day to achieve *in utero* growth rates, rather than 3.5–4.0 g/kg/day. There is a need to maintain appropriate energy: protein ratios.

○ Favours the intervention ○ Varies ○ Don't know	Increase in weight gain when adjusted for energy intake **Studies reporting the optimal amount of protein supplementation from or in addition to breastmilk fortifier or preterm formula** **Protein supplementation compared with no protein supplementation- low certainty evidence** Possible increase in *no faltering growth*/body composition (weight gain) **Protein supplementation compared with no protein supplementation- very low certainty evidence** Possible increase in *no faltering growth*/body composition (length gain; head circumference) Increase in duration of initial hospital stay Uncertain effect on necrotising enterocolitis No effect on time to full enteral feeds **High protein compared with moderate protein supplementation- high certainty evidence** Possible increase in *no faltering growth*/body composition (weight gain; length gain) No effect on faltering growth/body composition (head circumference) **High protein compared with moderate protein supplementation- moderate certainty evidence** Uncertain effect on necrotising enterocolitis, time to full enteral feeds, sepsis **High protein compared with moderate protein supplementation- low certainty evidence** No effect on mortality Increase in duration of initial hospital stay **High protein compared with low protein supplementation - very low certainty evidence** Uncertain effect on neurodevelopmental impairment, faltering growth/body composition (length) **Moderate protein compared with low protein supplementation- low certainty evidence** Possible increase in *no faltering growth*/body composition (length gain) Uncertain effect on duration of initial hospital stay **Moderate protein compared with low protein supplementation- very low certainty evidence** Uncertain effect on mortality, sepsis Possible increase in *no faltering growth*/body composition (weight gain) No effect on faltering growth/body composition (head circumference) Uncertain effect on necrotising enterocolitis **Balance of effects for Māori** No additional evidence available.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of enteral protein supplementation is small (<$0.20 per day) Requires additional dietetic resources which may limit its acceptability in some units **Resources required for Māori** No additional evidence available.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Costs are certain. **Certainty of evidence of required costs for Māori** No additional evidence available.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	There are no studies that assess the specific cost-effectiveness of additional enteral protein supplementation, particularly in the context of preterm infants. **Cost effectiveness for Māori** No additional evidence available.	

Equity

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Equity for Māori** Pēpi Māori are disproportionately affected by preterm birth and associated complications due to colonisation and ongoing inequities in health care. Without additional protein, breastmilk alone may not meet their nutritional needs, placing them at risk of poor growth and developmental delays. When protein supplementation is offered inconsistently or delayed due to systemic bias or resource gaps, these outcomes may worsen. Ensuring that whānau Māori have equitable access to supplementation, along with culturally safe information and support, is essential. This can help reduce health disparities and promote better lifelong outcomes for pēpi Māori and their whānau. **Equity for Pacific families** Pacific infants are also more likely to be born preterm and may encounter limited or inconsistent access to specialised nutrition support such as protein supplementation. Pacific families often value collective decision-making and may have unique feeding preferences but may not receive early or culturally responsive education about supplementation. Without adequate support, Pacific infants risk missing out on essential nutrients for brain and body development. Equity in this context means ensuring timely access to protein fortification and involving Pacific parents in feeding decisions through respectful, tailored communication that aligns with their cultural values. **Equity for underrepresented groups** Families from rural areas, migrant backgrounds or lower socioeconomic communities may face additional barriers to accessing consistent enteral protein supplementation. These include fewer neonatal resources, limited transport to tertiary hospitals and reduced access to culturally and linguistically appropriate support. Parents may not fully understand the purpose or benefits of supplementation, especially if they receive inconsistent messages from clinical staff. To ensure equity, guidelines must be applied consistently and education delivered in accessible ways. Standardising care while addressing structural barriers can help ensure all preterm infants receive the nutritional support needed for healthy development, regardless of where or to whom they are born.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No	Already in widespread use.	

○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Requires additional dietetic resources which may limit its acceptability in some units. Some parents decline supplementation, due the protein source being cow's milk protein. **Acceptability for Māori** No additional evidence available.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Already in widespread use. **Feasibility for Māori** No additional evidence available.	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
REQUIRED							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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