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Complete List of Authors:	Beker, Friederike; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Macey, Judith; University of Queensland, Mater Research Institute Liley, Helen; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Hughes, Ian; Gold Coast University Hospital Davis, Peter; The Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research Twitchell, Emily; Murdoch Childrens Research Institute, Clinical Sciences Research Jacobs, Susan; Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research
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The effect of smell and taste of milk during tube feeding of preterm infants (the TASTE trial): a protocol for a randomised controlled trial.

Friederike Beker[1,2], Judith Macey[1], Helen Liley[1,2], Ian Hughes[3], Peter G Davis[4,5], Emily Twitchell[5], Susan Jacobs[4,5].

[1] Mater Research Institute, University of Queensland, South Brisbane, Australia; [2] Neonatal Intensive Care Unit, Mater Mothers' Hospital, South Brisbane, Australia; [3] Gold Coast University Hospital, Southport, Australia; [4] Neonatal Intensive Care Unit and Newborn Research Centre, Royal Women's Hospital, Parkville, Australia; [5] Clinical Sciences Research, Murdoch Children's Research Institute, Parkville, Australia.

Corresponding author: Friederike Beker, Neonatal Intensive Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, Queensland 4101, Australia; email: friederike.beker@mater.org.au; phone: +61 7 3163 1955

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Abstract

Introduction Smell and taste of milk are not generally considered when tube feeding preterm infants. Preterm infants have rapid growth, particularly of the brain, and high caloric needs. Enteral feeding is often poorly tolerated which may lead to growth failure and long-term neurodevelopmental impairment. Smell and taste are strong stimulators of digestion and metabolism. We hypothesise that regular smell and taste during tube feeding will improve weight z-scores of very preterm infants at discharge from hospital.

Methods and analysis TASTE is a randomised, un-blinded two-centre trial. Infants born at <29 weeks' gestation and/or <1250g at birth and admitted to a participating neonatal intensive care unit are eligible. Randomisation occurs before infants receive 2hrly feeds for 24 hours. Infants are randomised to either smell and taste of milk with each tube feed or tube feeding without the provision of smell and taste. The primary outcome is weight z-score at discharge. Secondary outcomes include: days to full enteral feeds, duration of parenteral nutrition, rate of late-onset sepsis, post menstrual age at removal of nasogastric tube and at discharge from hospital, anthropometric data, and neurodevelopmental outcomes at two years of corrected age.

Ethics and dissemination Human Research Ethics Committees of Mater Misericordiae Ltd (trial reference number: HREC/16/MHS/112) and the Royal Women's Hospital (trial reference number: 17/21) last approved the trial protocol (Version 3; Date May 8th, 2017) and recruitment commenced in May 2017 and November 2017, respectively. The trial results will be published in a peer reviewed journal and will be presented at national and international conferences.

Trial registration number Australian and New Zealand Clinical Trials Registry: ACTRN12617000583347: supplementary file 1.

Strength and limitations of this trial

- This trial is the first adequately powered randomised trial to investigate the effects of smell and taste during tube feeding of very preterm infants.
- Blinding of the allocated intervention is not feasible, therefore an objective criterion for the primary outcome (weight z-score at discharge) was specified.
- Smelling and tasting of milk is an uncomplicated and potentially cost-effective intervention that may have a number of beneficial health effects such as improved weight gain and feed tolerance as well as a reduction in length of hospital stay.

Introduction

Background and rationale

Close to 7000 infants are born before term and admitted to neonatal intensive care units (NICUs) across Australia and New Zealand each year.(1) Preterm infants have an impaired ability to breathe, suck and swallow in a coordinated fashion. This immaturity presents a significant challenge to the provision of effective nutrition, commonly leading to postnatal growth failure.(2) Brain growth in the last four to eight weeks of gestation is extremely rapid and is crucial for later development. Malnutrition during a vulnerable phase of brain development leads to a reduced number of neurons and later behaviour, learning and memory problems. In preterm infants, this extremely rapid phase of brain growth occurs *ex utero* at a time when providing adequate nutrition is challenging. Thus, optimising postnatal growth may result in improved neurodevelopmental outcomes.(3)(4)

Taste and smell in the NICU

Pleasant odours and tastes, such as those encountered with a good meal or a familiar person, have an enormous influence on our own daily well-being. Despite our own understanding of the role of taste and smell in our lives, preterm infants are usually only exposed to the smell of the mother's skin or breast milk once the infant is well enough to be removed from the incubator for skin-to-skin care and breast feeding. The frequency and duration of such skin-to-skin care is dependent upon the philosophy of the NICU and individual staff.(5) The infant's most common smell experience is often restricted to the odours of the direct environment, commonly excrement and antiseptics. Taste experiences may be dominated by rubber and plastic from feeding and breathing tubes in the mouth or associated with discomfort and pain, when breastmilk or sucrose is given for pain relief.(6)(7) Thus, preterm infants are not only deprived of the pleasures of smell and taste but it is also possible that placement of milk feeds directly into the stomach via a feeding tube without any food anticipation may impact on metabolism and early nutritional learning.

Food anticipation and the cephalic phase response

Anticipation of food activates the digestive system. Pavlov famously explored and described this phenomenon over a hundred years ago.(8) Sham feeding, the mere taste of food in the oral cavity of dogs, led to the production of gastric secretions. Pavlov also confirmed that the sight of food or even unrelated signals such as the sound of a bell could elicit the same strong response, as long as the dog was conditioned and knew that the bell was related to food intake. In an experiment analogous to the gastric feeding of preterm infants, Pavlov also placed bread into the stomach of his dogs through a tube, without the dog being aware.

The bread remained undigested in the dogs' stomachs for up to one hour. Furthermore, Pavlov stated that a food ingested by a dog only acted as a stimulus when it "suited the dog's taste". He concluded that the response of the stomach to the anticipation of food depended on the presence of appetite.(8,9) This activation of the digestive system by anticipation of food has been named the 'cephalic response'.(10,11) Decades of ongoing research have revealed that the cephalic response plays an even more complex role in nutrition, from early nutritional learning to improved nutrient absorption, increased stomach and gut motility, anticipatory secretion of insulin with tighter blood glucose control, and the release of appetite, digestive and metabolic hormones such as leptin, ghrelin, insulin and gastrin.(12,13)

Smell and taste in preterm infants

Preterm infants are believed to have flavour perception. Functional taste receptors are present from 18 weeks' postmenstrual age (PMA) and flavour perception is established around 24 weeks' PMA. Changes in tissue oxygenation by near-infrared spectroscopy have been detected in term and preterm infants >32 weeks' PMA in response to odours, with different responses occurring to odours rated as pleasant or unpleasant.(14,15)

Amniotic fluid and breast milk have flavours that reflect the foods, spices, and beverages consumed by the mother. (16,17) Infants exposed to those flavours during late pregnancy and early infancy exhibit food preference to such flavours, some persisting into adulthood.(18) It is well known that toddlers prefer the flavour composition they have been exposed to *in utero* and during breast feeding (the mother's diet) as infants.(19) Similarly, exposure to alcohol in late pregnancy makes alcohol more palatable in later life and even increases intake.(20,21) It is also suspected that intra-uterine and postnatal exposure to fructose increases the rate of obesity later by altering feeding behaviour and appetite control as well as neuroendocrine function.(22)

Early priming of the olfactory and gustatory systems is critical, as the ability to 'taste' chemical compounds guides the amount of food eaten and is imperative for the evaluation of food quality. Once food intake is expected or commenced, the brainstem and higher centres activate the cephalic phase response and release appetite hormones in saliva.(23) These salivary hormones are postulated to play a role in metabolism; indeed, impaired oral nutrient sensing is associated with increased energy intake and a greater body mass index.(24)

Preterm infants do not have the opportunity to experience the most basic of stimuli and sensation associated with feeding: hunger, satiety, taste and smell. NICU clinicians regulate feed times, frequency and volumes of feed. Milk is delivered through a gastric tube until infants are mature enough to attempt breastfeeding bypassing the gustatory and olfactory receptors that are involved in stimulating many of the preprandial responses outlined above.

Relevant clinical trials in the NICU environment.

There are three prior studies in preterm infants in which taste may have been a variable affecting time to full enteral feeds. Rodriguez et al. (2011) reported as a secondary outcome in a randomised study of 16 extremely low birth weight (ELBW; <1000g) infants that infants receiving 2 hourly oropharyngeal colostrum for 48 hours in the first days after birth reached full enteral feeds significantly faster than the control group, receiving water instead of colostrum.(25) However, another similar study of 48 ELBW infants who received 3 hourly oropharyngeal colostrum for three days in the first days after birth, did not find any difference

in time to full enteral feeds between the intervention and control groups.(26) Both studies provided oropharyngeal colostrum for only a few days with the primary outcome being immunological effects. Neither of the studies reported if the colostrum was given in combination with tube feeds.

Another study investigated the effect of 14 days of a sweetened pacifier versus a plain pacifier on weight gain in infants born less than 34 weeks' PMA with a birth weight of more than 1250g.(27) There were no statistically significant differences between groups.

A pilot trial, preceding this study, demonstrated that smell and taste with every tube feed reduced the time to full enteral feeds in very low birthweight (VLBW, <1500g) infants. Infants who had been exposed to regular smell and taste of their milk feed also had higher weight z-scores at discharge – a crucial outcome, as higher weight z-scores are associated with better long-term neurodevelopmental outcomes.(28)(3)

Following this pilot study, Bloomfield et al. included 'smell and taste with tube feeding' into their study protocol examining early feeding practices in moderate to late preterm infants and their effect on nutritional, metabolic and neurodevelopmental outcomes.(29) The same group also recently published a Cochrane Database of Systematic Reviews protocol to examine the effects of smell and taste with tube feeding.(30)

Summary and rationale

Few NICUs routinely provide infants with the smell and/or taste of their milk with tube feeds, despite the assumption that premature infants can taste and smell, and despite our own regular indulgence in smell and taste perception. It is common for smell and/or taste to be provided on an ad hoc basis, for pain relief, mouth care and/or occasionally with tube feeding. Smell and taste strongly elicit the cephalic phase response and may have the potential to improve milk tolerance, digestion and metabolism in very low birth weight infants. The few published studies that investigated the effects of taste on tube feeding expose infants only for a few days, include only late preterm infants or have small sample sizes. This trial is powered to demonstrate the effects of smell and taste of milk with every tube feed on the weight z-score at discharge. Other important outcomes include: length of stay in hospital, duration of parenteral nutrition, and late onset sepsis.

Methods and analysis

Trial design and setting

The TASTE trial is a two centre, parallel-group randomised superiority trial, including preterm infants admitted to the NICU at the Mater Mothers' Hospital (MMH) in Brisbane and the NICU at the Royal Women's Hospital (RWH) in Melbourne, both in Australia.

Participant and public involvement

Feedback and discussions from families enrolled in the pilot study aided in the development of the research question and outcome measures as well as in assessing the burden of the intervention. Governance regulations did not allow for the involvement of relevant patient families in the planning of or in the recruitment to this study. Results of this study will be published on the MMH and RWH website and social media.

Eligibility criteria

Inclusion criteria: Male and female preterm infants born at less than 29 weeks' PMA and/or birth weight less than 1250 g with written informed parental/guardian consent. Consent must be obtained before infants are fed regularly (2hrly or more frequent feeds for less than 24 hours).

Exclusion criteria: Congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma at birth (e.g.: anal atresia), oesophageal atresia; congenital conditions leading to impaired growth, e.g.: trisomy 21, trisomy 18, or salt wasting enteropathy.

Interventions

Treatment Group: Infants in the treatment group receive smell and taste with every tube feed by the bedside nurse:

- smell: a drop of milk on a gauze swab will be placed as close as possible to the infant's nose, without touching. The intervention will be ceased at 32 weeks' PMA in order to comply with safe sleeping guidelines.
- taste: a cotton wool bud soaked in milk will be placed on the infant's tongue if the infant is less than 32 weeks' PMA. From 32 weeks' PMA, 0.2 ml of milk will be given to the infant directly on the tongue.

If the infant is asleep, the smell is given as described above. For the taste, the milk is held onto the infants' lips. If the infant shows any interest, the milk (cotton bud or syringe) is placed in the infants' mouth.

Control Group: infants receive routine care and do not have any milk in the mouth with tube feeding. Milk for tasting with nasogastric tube feeds can only be given if prescribed by a speech pathologist, usually not before 38 weeks' PMA. The control group resembles routine care and was therefore chosen as comparator.

All infants, treatment and control group, are allowed to suck feed, receive sucrose, have skin-to-skin care and other contact with their parents, smell blankets provided by parents and/or suck on pacifiers at any time if parental consent is provided. The trial ends with the removal of the nasogastric tube. Parents can decide if they want to give oral milk with tube feeds or not if an infant is discharged home on nasogastric tube feeds.

Withdrawal of consent leads to routine care currently practiced in the NICUs, that is nasogastric tube feeding without the provision of smell and taste of milk. Therefore, withdrawal of consent only in the treatment group leads to a change in the infant's care.

Bedside instructions for both allocation groups are placed at the cot side to ensure adherence to the trial protocol. Research nurses check regularly that instructions remain at the bedside and that nurses adhere to those instructions. Site investigators ensure adherence to the trial protocol.

Primary outcome

- Weight z-score at discharge from hospital.

Secondary outcomes

- Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours)
- Duration of parenteral nutrition (days) total, and first episode

- Rate of late onset sepsis, diagnosed after 24 hrs of life in a symptomatic infant with positive blood culture, cerebrospinal fluid, or sterile collected urine, treated for a minimum of 5 days with antibiotics. Potential contaminants (e.g. coagulase – negative staphylococci) will be included if the infant in addition has a neutrophil left shift of ≥ 20 % and/or C – reactive protein is ≥ 10 mg/L.
- Cumulative duration of antibiotic therapy (days)
- PMA at removal of nasogastric tube
- PMA at discharge home from hospital
- Type of feeding at different time points (e.g.: type of milk given)
- Rate and severity of retinopathy of prematurity
- Rate and severity of necrotizing enterocolitis
- Rate and severity of intraventricular haemorrhage
- Rate of chronic lung disease at 36 weeks PMA
- Spontaneous intestinal perforation
- Rate of treated patent ductus arteriosus
- Anthropometric data at different time points
    - Head circumference at 28 days, 36 weeks' PMA, at discharge home
    - Length at 36 weeks' PMA, at discharge home
- Respiratory support in hours (continuous positive airway pressure or high flow nasal cannula, and endotracheal respiratory support)
- Data will be collected from infants assessed in the long term follow up program at 1 and 2 years corrected age (CA) (e.g.: anthropometric data, respiratory support, type of feeding, cerebral palsy, level within the Gross Motor Function Classification System, hearing and vision assessments, Bayley III results)
- Rate of breast feeding at 3, 6 and 12 months of CA.

Participant timeline

The schedule of enrolment, interventions and assessments is presented in table 1.

	Trial Period									
	Enrolment	Allocation	Post allocation							Closeout
Time point	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_x
Enrolment:										
Eligibility screen	x									
Informed consent	x									
Allocation		x								
Interventions:										
Smell and taste with tube feeding			●	—	●					
Routine care			●	—	●					

Assessments:										
Baseline variables	x	X								
Primary outcome					x					
Secondary outcomes				x	x	x	x	x	x	x

Table 1 Schedule of enrolment, interventions and assessments.
–t1: before allocation; t0: time of allocation/randomisation; t1: time to full enteral feeds; t2: time of full enteral feeds; t3: time of discharge; t4: 3 months CA; t5: 6 months CA; t6: 1 year CA; t7: 2 years CA; tx: 2 years CA for infants eligible for the long term follow up program, 1 year for infants not eligible for the follow up program but parents consented to be contacted for breast feeding rates, time of discharge home from hospital for all other infants.

Sample size calculation

Sample size calculation for the TASTE trial is based on detecting an improvement in weight z-score at discharge from a mean of -0.31 to -0.1 with a type I error of 5% and 90% power. Multiples are randomised together to the same study group. Therefore, twins and triplets were considered in the sample size calculation with a mother's infants from one pregnancy defined as a cluster. The pilot study had a mean cluster size of 1.08 with an intra-cluster correlation coefficient of 0.35 and a standard deviation in weight z-score at discharge of 0.58. Given these criteria, based on a two-sided generalised estimating equations (GEE) model, the required sample size was calculated to be 165 for each group.(31) This sample size is inflated and controls for clustering within multiple births.

Recruitment

The study team member will identify potential participants for the trial and approach their parents for written consent. Parents will not be approached for consent antenatally, but they may be informed about the trial. However, if parents indicate that they do want their infant to participate in the trial, a participant information and consent form (PICF – supplementary file 2) will be provided.

Participants will be actively recruited after birth and parents approached for written consent by a study team member. Potential participants for the trial will be identified from the inpatient list of the NICUs on a daily basis. Parents will be approached when they have recovered from the stress of birth and when they are able to consent. Parents will have the ability to consider participation, discuss the trial with their friends, family and local general practitioner, ask questions and decide to consent or not to the trial without any consequences to the care of their infant. Clinical care of the infant will always take priority over any research study and wherever possible, consent will be obtained by a member of the study team not directly involved in the infant's clinical care.

Randomisation

A randomisation sequence of treatment or control with variable block sizes (2-6) was generated by IH using the ralloc command of Stata 14 (College Station, TX, USA). Randomisation is stratified by site, sex and PMA (<27 weeks' PMA and >/= 27 weeks' PMA). Each participating centre is provided with sequentially numbered, sealed, opaque, envelopes containing the assigned treatment allocation. The envelope is opened after parental consent

has been given, immediately before the trial commences. One envelope is opened for each set of multiple births.

Blinding

Treatment allocation and the primary outcome are not blinded in this trial. Blinding of the treatment allocation was considered but it was concluded that it was not feasible for the intervention tested. A robust primary outcome was chosen with the aim to prevent observer bias while it is acknowledged that the potential for "treatment leakage" still exists. To mitigate this concern, we will ensure that clinical care teams, researchers, and parents/caregivers are provided education regarding the importance of maintaining the integrity of the randomisation of the trial.

The following secondary outcomes are assessed by clinicians blinded to the infant's allocated group: retinopathy of prematurity, x-ray findings required to determine the severity of necrotizing enterocolitis, intraventricular haemorrhage, presence of chronic lung disease, spontaneous intestinal perforation, respiratory support in hours, outcomes from long term follow up program from eligible infants at 1 and 2 years CA.

Data management

Data will be sourced from each participant's observation chart, clinical care team notes, medical records and verbally from parents. Each infant will be assigned a study number and data will be collected under that study number. Data will be de-identified when entered onto a paper case record form, then transferred by the data manager to an excel spread sheet and stored on a password protected computer on the MMH computer network. Each data set will be checked by the principal investigator for plausibility and data range checks are applied in the database as appropriate.

The MMH Human Research Ethics Committee reviewed the protocol and the pilot study and advised that a data monitoring committee, an interim analysis and stopping guidelines were not required for this trial.

Statistical methods

Statistical analysis will be performed by the authors Hughes and Beker with assistance of other study group members. Data will be exported from an excel spreadsheet to a statistical package for analysis (Stata; College Station, TX, USA). Data will be analysed on an intention to treat basis. All randomised infants will be included in the primary analysis, unless consent has been withdrawn. Data of deceased infants will be included in the analysis if the respective outcome is achieved.

Univariate and multivariable GEE analyses will be used for the primary outcome, weight z-scores at discharge from hospital, and other continuous secondary outcome measures. Time to full enteral feeds will be analysed using a multilevel survival analysis (mestreg command in Stata).(28) Secondary outcomes with categorical data will be analysed using a mixed effects logistic regression (melogit Stata command). Subgroup analysis will be performed based on sex and PMA for the primary outcome and selected secondary outcomes.

All outcomes will be assessed against a hypothesis of superiority.

Harms
Principal investigators / their delegates will be responsible for all safety reporting. Study infants are at high risk and rely on intensive care of their medical problems. Deaths of study infants will be reported to the approving HREC and governance department within 24 hours of knowing by the site principal investigator / delegate. This includes adjudication of the likelihood of the event being related to the involvement in this trial.

In both participating NICUs, clinical incidents are reviewed by the Patient Safety Units. Trends and concerns regarding patient safety are analysed and the results shared with the NICU's to prevent patient harm. Principal investigators will be informed by the Patient Safety Units should there be any concern in regards to the safety of the TASTE trial. The TASTE trial has no established external study monitoring committee.

Discussion

Exposure of preterm infants to the smell and taste of milk is infrequently considered by clinicians or researchers. Smell and taste of food prepares the body for food intake, digestion and metabolism and may improve important clinical outcomes of preterm infants that are challenged by sub-optimal weight gain and poor enteral milk tolerance.(28)

TASTE is the first adequately powered trial to test the effect of smell and taste in very preterm infants. Use of a placebo in the control group has proven difficult. Pavlov's experiments with dogs have demonstrated that multiple sensory inputs, not related to food intake, can elicit a cephalic phase response. The offer of normal saline or water taste on a cotton bud or via syringe is therefore not appropriate for the control group. Due to the lack of blinding a robust primary outcome (weight z-scores at discharge from hospital) was selected.

If smell and taste with tube feeding is shown to beneficial for very preterm infants, this straight forward intervention may easily be adopted by NICUs and not only improve clinical outcomes, but also save costs and resources.

Ethics and dissemination

Research ethics
The HRECs of MML and RWH approved of the study protocol (version 3, 8th of May 2017), trial reference number HREC/16/MHS/112 and trial reference number 17/21, respectively. Both hospitals also granted governance approval.

Dissemination of results
The results of the trial will be published in a peer-reviewed journal and will be presented at national and international conferences. Authorship will be determined in line with the International Committee of Medical Journal Editors guidelines. A data sharing agreement will be in place to allow all study group members to access the final trial dataset. Access to the participant-level dataset may be granted if an appropriate data sharing agreement is arranged.

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Author contributions

FB conceived of the study. FB, IH and SEJ developed the study design and FB, HL, PGD, JM, ET and SEJ facilitated study implementation. IH provided statistical expertise in clinical trial design and together with FB planned the statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript. The primary trial sponsor is Mater Misericordiae Ltd, contact: CEO Mater Research, Governance Office, email: research.governance@mater.uq.edu.au, phone: +61 7 3163 3769. The trial sponsors have approved of the study protocol, but have no role in study design, in collection, management, analysis, and interpretation of data, in writing of the report, and the decision to submit the report for publication.

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Competing interest statement

Peter G Davis received salary support from Australia's national research funding agency. Neither the principal investigator nor the other investigators have any other financial or other competing interests for the overall trial and each study site to declare.

GLOSSARY OF ABBREVIATIONS

AE: adverse event; CA: corrected age; d: day; ELBW: extremely low birth weight; GEE: generalised estimate equations; HREC: Human Research Ethics Committee; kg: kilogram; L: litre; mg: milligram; ml: millilitre; MMH: Mater Mothers' Hospital; NICU: neonatal intensive care unit; PMA: postmenstrual age; RWH: Royal Women's Hospital; SAE: serious adverse event; VLBW: very low birth weight

Supplementary file 1

World Health Organization Trial Registration Data Set:

Data category	Information
Primary registry and trial identifying number	anzctr.org.au ACTRN12617000583347
Date of registration in primary registry	26 April, 2017
Secondary identifying numbers	Universal trial number: U1111-1192-6122
Source(s) of monetary or material support	Mater Research Institute Royal Australasian College of Physicians and Paediatricians – Queensland Branch
Primary sponsor	Mater Misericordiae Limited, South Brisbane, QLD, Australia
Secondary sponsor(s)	Royal Women's Hospital, Grattan, Victoria, Australia
Contact for public queries	Dr Friederike Beker, Neonatal Critical Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, QLD 4101, Australia Phone: +61 7 3163 1955; email: friederike.beker@mater.org.au
Contact for scientific queries	Dr Friederike Beker, contact as above
Public title	Effect of smell and taste to improve nutrition in very preterm babies
Scientific title	Smell and taste with tube feeding to improve nutrition in very preterm infants: a randomised controlled trial.
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Prematurity, growth failure, milk intolerance
Intervention(s)	smell and taste of milk (mothers' breast milk, pasteurised donor breast milk or formula) with tube feeding - with every feed for the duration of the feed <32 weeks PMA until 32 weeks PMA: cotton bud soaked in milk offered for sucking and drop of milk on cotton pad placed close to the infant's nose >32 weeks PMA until removal of nasogastric tube or discharge: 0.2 ml of milk given orally with a feeding syringe
Key inclusion and exclusion criteria	Ages eligible for study / inclusion criteria: < 29 weeks PMA and/or less than 1250 g birth weight Sexes eligible for study: both Can healthy volunteers participate? Exclusion criteria: infants with congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma after birth (e.g.: anal atresia), oesophageal atresia. 2. Congenital conditions leading to impaired growth: e.g.: trisomy 21, trisomy 18, salt wasting enteropathy.
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: open (masking not used) Primary purpose: treatment

	Phase: not applicable
Date of first enrolment	May 2017
Target sample size	330
Recruitment status	Recruiting
Primary outcome(s)	Weight z-scores at discharge home assessed by calibrated digital scales.
Key secondary outcomes	Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours), assessed by review of feeding records Duration of parenteral nutrition (days) total. Duration of antibiotics (days) total. Episodes of late onset sepsis. PMA at discharge home from hospital.

Document Title:	Research Patient Smell and taste to improve nutrition in very preterm infants: a randomized controlled trial
Unit Record No.:	
Surname:	
Given Names:	
DOB:	

Participant Information Sheet

Interventional Study - *Parent/Guardian consenting on behalf of participant*

Title	Taste and smell to improve nutrition in very preterm infants: a randomised controlled trial
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit at the Mater Mothers' Hospital

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for your baby to take part in this research project because they were born extremely premature. The research project is testing whether smelling and tasting milk before each feed improves nutrition and digestion. The only change in your baby's care will be that the baby may be given milk to taste and smell at the beginning of every tube feed.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your baby to take part in the research.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more. Before deciding whether or not the child will take part, you might want to talk about it with a relative, friend or the child's local doctor.

Participation in this research is voluntary. If you do not wish your baby to take part, they do not have to. Your baby will receive the best possible care whether or not they take part.

If you decide you want the child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you

- understand what you have read,
- consent to your baby taking part in the research project,
- consent for your baby to have the tests and treatments that are described and
- consent to the use of your baby's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Babies born extremely premature initially rely on nutrition given through the vein because their gut is immature and milk is not easily digested. When feeds are started, milk is routinely given directly into the stomach through a tube. We use a tube because preterm babies cannot yet coordinate sucking, swallowing and breathing.
We already know that preterm babies do not tolerate milk feeds very well. Many studies have tried to improve milk tolerance but there is still room to improve.

With this study we are investigating whether preterm babies tolerate milk better if they are able to smell and taste their milk before and during the time milk is given into their stomach via a tube. This is important because we know that preterm babies grow better when they are able to tolerate their milk. Regular smell and taste is not usually considered in the care of preterm babies.

We have already completed a smaller trial investigating the effects of smell and taste in preterm babies and are required to repeat it in a larger number of babies.

We hope to improve the care of preterm babies in the future. Smell and taste of milk could easily be included in routine care if it were shown to improve milk tolerance.

This research has been initiated by the study doctor, Dr Friederike Beker.

This research has been funded by Mater Research Institute.

3 What does participation in this research involve?

➤ Consent
Your baby will only participate in the study if you agree and have signed the consent form.

➤ Initial steps
We will have checked if your baby is eligible to participate in the study. Your baby will be excluded if he/she has significant problems with his/her gut from birth and/or if he/she has a medical condition that is known to affect growth.

Your baby can participate in this study if you sign the consent form.

Enrolment in this study will not affect participation in other studies.

All babies will be allocated to one of two groups by chance. One group of babies will receive routine care, the other group will receive the intervention (smell and taste their milk before each feed).

➤ Intervention

Babies in one study group will smell and taste their milk before each feed, starting after you have consented. A cotton wool pad with a drop of milk will be placed in front of their nose. In addition, a cotton wool bud soaked in milk or a small feeding syringe will be used to provide taste by touching the tongue with milk. Cotton wool buds and feeding syringes are used in routine care for the application of medication.

The control group will not smell and taste their milk with tube feeding as is currently the common practice in the nursery. The intervention will continue until the nasogastric tube is removed. All babies in the treatment or control group may have breast feeds, dummies, sucrose for pain relief, cuddles with parents and/or parents scent at any time at the discretion of the treating clinical team.

Your baby will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same and to reduce bias it is important that each participant is put into a group by chance (random).

This research project has been designed in this way to make sure the researchers interpret the results in a fair and appropriate way and avoid study doctors or participants jumping to conclusions.

There are no additional costs associated with participation in this research project, nor will you or the participant be paid. All medical care required as part of the research project will be provided to your baby free of charge.

4 What does my baby have to do?

Your baby will be randomised to either the treatment or intervention group. According to randomisation, your baby will receive routine care or will taste and smell the milk before each tube feed. Data will be recorded about your baby's progress but there are no additional commitments required for your baby.

5 Other relevant information about the research project

A total of 330 preterm babies will take part in this research project, 165 in each group. Babies will be recruited at the Neonatal Critical Care Unit at the Mater Mothers' Hospital and at the Neonatal Intensive and Special Care at the Royal Women's Hospital, Melbourne. This project is a follow up from the previous pilot study called 'Smell and taste to improve nutrition in preterm infants: a randomised controlled pilot trial' and involves researchers from the Mater Mothers' and Royal Women's Hospitals and from the Mater Research Institute.

6 Does my baby have to take part in this research project?

Participation in any research project is voluntary. If you do not wish your baby to take part, they do not have to. If you decide that they may take part and later change your mind, you are free to withdraw your baby from the project at any stage.

If you do decide that your baby can take part, you will need to sign this Parent Information and Consent Form and you will be given a copy to keep.

Your decision that your baby may or may not take part or that they may take part and then be withdrawn will not affect their routine treatment, relationship with those treating them or their relationship with The Mater Mothers' Hospital.

7 What are the alternatives to participation?

Your baby does not have to take part in this research project to receive full treatment at this hospital.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the child will receive any benefits from this research. However, possible benefits may include better tolerance of milk feeds and/or improved growth.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects, however, we are not aware of any issues associated with smell and taste of milk. In case your baby experiences any discomfort or side effects, or you are worried about them, talk with any of the staff. We will take your concerns seriously and will manage any discomfort and concerns related to the study.

If you or your baby becomes upset or distressed as a result of participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who is not members of the research project team. This counselling will be provided free of charge.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want your baby to continue in the research project. If you decide to withdraw your baby, their study doctor will make arrangements for their regular health care to continue.

11 Can the child have other treatments during this research project?

Your baby can have all other treatment during the research project. No restrictions are necessary.

12 What if I withdraw the child from this research project?

If you decide to withdraw your baby from the project, please notify a member of the research team before you withdraw them. This notice will allow that person or the research supervisor to discuss further any health risks or special requirements linked to withdrawing.

If you do withdraw your baby from the study, personal information already collected will be retained but no further data will be collected. This is to ensure that the results of the research project can be measured properly and comply with law. If you do not want the study team to use already collected data, you must tell them before your baby joins the research project.

You also have the option to withdraw your baby from the study procedure only and allow the research team to continue with data collection past the time point of withdrawal from the study procedure.

Mater Research

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects.

14 What happens when the research project ends?

Babies born at less than 28 weeks gestation or below 1000g are routinely offered developmental follow up at 1 and 2 years of age. We would like to collect data from those follow up assessments.
If you give us permission, we will contact you at ~ 1 year corrected age to ask how your baby is doing and about how long you breast fed.

Part 2 How is the research project being conducted?

15 What will happen to information about the child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your baby for the research project. Any information obtained in connection with this research project that can identify your baby will remain confidential.

Data will be stored de-identified under a study number on a password locked work computer. A list linking the study number to your baby's personal details will be kept in a locked cupboard in the Research Office. Your baby's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your baby may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your baby's participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums (e.g., conferences, journal articles, teaching presentations). In any publication and/or presentation, information will be provided in such a way that your baby cannot be identified, except with your permission. Confidentiality will be maintained as results will only be published in a de-identified manner.

Information about your baby's participation in this research project may be recorded in their health records.

In accordance with relevant Australian and Queensland privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member whose name appears at the end of this document if you would like to access your baby's information.

Any information obtained for the purpose of this research project that can identify your baby will be treated as confidential and securely stored. It will be disclosed only with your permission or as required by law.

16 Complaints and Compensation

If your baby suffers as a result of this research project, appropriate medical treatment for your baby will be arranged. If your baby is eligible for Medicare, they can receive any medical treatment required free of charge as a public patient in any Australian public hospital.

17 Who is organising and funding the research?

This research project is being organised and funded by the Mater Research Institute.

No member of the research team will receive a personal financial benefit from your baby's involvement in this research project (other than their ordinary wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Mater Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 07 3163 1918 or any of the following people:

Mater Research Nurse	Phone: 07 3163 8543
Human Research Ethics Committee	Phone: 07 3163 1585

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.
A copy of the information sheet and consent form is for you to keep.

Consent Form – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital, South Brisbane

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my baby's doctors, other health professionals or hospitals outside this hospital to release information to the study team concerning my baby's disease and treatment for the purpose of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

☐ I freely agree to my baby's participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

☐ I agree to the collection of the results of my baby's 1 and 2 year follow-up developmental assessment (if performed)

☐ I agree to be contacted by a research nurse when my baby is 1 year old about the duration of breast feeding. I can change my decision any time.

I understand that I will be given a signed copy of this document to keep.

Name of Baby (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Name of Witness* to Parent/Guardian Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Form for Withdrawal of Participation – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital

Declaration by Parent/Guardian

I wish to withdraw the child from participation in the above research project and understand that such withdrawal will not affect their routine treatment, relationships with those treating them or the relationship with *the Mater Mothers' Hospital.*

I agree to data collection to continue past withdrawal from the study procedure: ☐ yes; ☐ no

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Description of circumstances:

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name	1

		of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1, sup 1
Protocol version	#3	Date and version identifier	1+9
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and	7

		statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	N/A

emergency unblinding		permissible, and procedure for revealing a participant's allocated intervention during the trial	
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1+9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	N/A

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public,	1+9

		and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7, sup 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

The effect of smell and taste of milk during tube feeding of preterm infants (the TASTE trial): a protocol for a randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027805.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Apr-2019
Complete List of Authors:	Beker, Friederike; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Macey, Judith; University of Queensland, Mater Research Institute Liley, Helen; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Hughes, Ian; Gold Coast University Hospital Davis, Peter; The Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research Twitchell, Emily; Murdoch Childrens Research Institute, Clinical Sciences Research Jacobs, Susan; Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care, Nutrition and metabolism
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NUTRITION & DIETETICS, Nutritional support < GASTROENTEROLOGY

The effect of smell and taste of milk during tube feeding of preterm infants (the TASTE trial): a protocol for a randomised controlled trial.

Friederike Beker[1,2], Judith Macey[1], Helen Liley[1,2], Ian Hughes[3], Peter G Davis[4,5], Emily Twitchell[5], Susan Jacobs[4,5].

[1] Mater Research Institute, University of Queensland, South Brisbane, Australia; [2] Neonatal Intensive Care Unit, Mater Mothers' Hospital, South Brisbane, Australia; [3] Gold Coast University Hospital, Southport, Australia; [4] Neonatal Intensive Care Unit and Newborn Research Centre, Royal Women's Hospital, Parkville, Australia; [5] Clinical Sciences Research, Murdoch Children's Research Institute, Parkville, Australia.

Corresponding author: Friederike Beker, Neonatal Intensive Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, Queensland 4101, Australia; email: friederike.beker@mater.org.au; phone: +61 7 3163 1955

Word count: 3717

Key words: neonatology, paediatrics, nutrition, tube feeding, growth

Abstract

Introduction Smell and taste of milk are not generally considered when tube feeding preterm infants. Preterm infants have rapid growth, particularly of the brain, and high caloric needs. Enteral feeding is often poorly tolerated which may lead to growth failure and long-term neurodevelopmental impairment. Smell and taste are strong stimulators of digestion and metabolism. We hypothesise that regular smell and taste during tube feeding will improve weight z-scores of very preterm infants at discharge from hospital.

Methods and analysis TASTE is a randomised, un-blinded two-centre trial. Infants born at <29 weeks' gestation and/or <1250g at birth and admitted to a participating neonatal intensive care unit are eligible. Randomisation occurs before infants receive 2hrly feeds for 24 hours. Infants are randomised to either smell and taste of milk with each tube feed or tube feeding without the provision of smell and taste. The primary outcome is weight z-score at discharge. Secondary outcomes include: days to full enteral feeds, duration of parenteral nutrition, rate of late-onset sepsis, post menstrual age at removal of nasogastric tube and at discharge from hospital, anthropometric data, and neurodevelopmental outcomes at two years of corrected age.

Ethics and dissemination Human Research Ethics Committees of Mater Misericordiae Ltd (trial reference number: HREC/16/MHS/112) and the Royal Women's Hospital (trial reference number: 17/21) last approved the trial protocol (Version 4.2; Date December 18th, 2018) and recruitment commenced in May 2017 and November 2017, respectively. The trial results will be published in a peer reviewed journal and will be presented at national and international conferences.

Trial registration number Australian and New Zealand Clinical Trials Registry: ACTRN12617000583347: supplementary file 1.

Strength and limitations of this trial

- This trial is the first adequately powered randomised trial to investigate the effects of smell and taste during tube feeding of very preterm infants.
- Blinding of the allocated intervention is not feasible, therefore an objective criterion for the primary outcome (weight z-score at discharge) was specified.
- Smelling and tasting of milk is an uncomplicated and potentially cost-effective intervention that may have a number of beneficial health effects such as improved weight gain and feed tolerance as well as a reduction in length of hospital stay.

Introduction

Background and rationale

Close to 7000 infants are born before term and admitted to neonatal intensive care units (NICUs) across Australia and New Zealand each year.(1) Preterm infants have an impaired ability to breathe, suck and swallow in a coordinated fashion. This immaturity presents a significant challenge to the provision of effective nutrition, commonly leading to postnatal growth failure.(2) Brain growth in the last four to eight weeks of gestation is extremely rapid and is crucial for later development. Malnutrition during a vulnerable phase of brain development leads to a reduced number of neurons and later behaviour, learning and memory problems. In preterm infants, this extremely rapid phase of brain growth occurs *ex utero* at a time when providing adequate nutrition is challenging. Thus, optimising postnatal growth may result in improved neurodevelopmental outcomes.(3,4)

Taste and smell in the NICU

Pleasant odours and tastes, such as those encountered with a good meal or a familiar person, have an enormous influence on our own daily well-being. Despite our own understanding of the role of taste and smell in our lives, preterm infants are usually only exposed to the smell of the mother's skin or breast milk once the infant is well enough to be removed from the incubator for skin-to-skin care and breast feeding. The frequency and duration of such skin-to-skin care is dependent upon the philosophy of the NICU and individual staff.(5) The infant's most common smell experience is often restricted to the odours of the direct environment, commonly excrement and antiseptics. Taste experiences may be dominated by rubber and plastic from feeding and breathing tubes in the mouth or associated with discomfort and pain, when breastmilk or sucrose is given for pain relief.(6,7) Thus, preterm infants are not only deprived of the pleasures of smell and taste but it is also possible that placement of milk feeds directly into the stomach via a feeding tube without any food anticipation may impact on metabolism and early nutritional learning.

Food anticipation and the cephalic phase response

Anticipation of food activates the digestive system. Pavlov famously explored and described this phenomenon over a hundred years ago.(8) Sham feeding, the mere taste of food in the oral cavity of dogs, led to the production of gastric secretions. Pavlov also confirmed that the sight of food or even unrelated signals such as the sound of a bell could elicit the same strong response, as long as the dog was conditioned and knew that the bell was related to food intake. In an experiment analogous to the gastric feeding of preterm infants, Pavlov also placed bread into the stomach of his dogs through a tube, without the dog being aware.

The bread remained undigested in the dogs' stomachs for up to one hour. Furthermore, Pavlov stated that a food ingested by a dog only acted as a stimulus when it "suited the dog's taste". He concluded that the response of the stomach to the anticipation of food depended on the presence of appetite.(8,9) This activation of the digestive system by anticipation of food has been named the 'cephalic response'.(10,11) Decades of ongoing research have revealed that the cephalic response plays an even more complex role in nutrition, from early nutritional learning to improved nutrient absorption, increased stomach and gut motility, anticipatory secretion of insulin with tighter blood glucose control, and the release of appetite, digestive and metabolic hormones such as leptin, ghrelin, insulin and gastrin.(12,13)

Smell and taste in preterm infants

Preterm infants are believed to have flavour perception. Functional taste receptors are present from 18 weeks' postmenstrual age (PMA) and flavour perception is established around 24 weeks' PMA. Changes in tissue oxygenation by near-infrared spectroscopy have been detected in term and preterm infants >32 weeks' PMA in response to odours, with different responses occurring to odours rated as pleasant or unpleasant.(14,15)

Amniotic fluid and breast milk have flavours that reflect the foods, spices, and beverages consumed by the mother.(16,17) Infants exposed to those flavours during late pregnancy and early infancy exhibit food preference to such flavours, some persisting into adulthood.(18) It is well known that toddlers prefer the flavour composition they have been exposed to *in utero* and during breast feeding (the mother's diet) as infants.(19) Similarly, exposure to alcohol in late pregnancy makes alcohol more palatable in later life and even increases intake.(20,21) It is also suspected that intra-uterine and postnatal exposure to fructose increases the rate of obesity later by altering feeding behaviour and appetite control as well as neuroendocrine function.(22)

Early priming of the olfactory and gustatory systems is critical, as the ability to 'taste' chemical compounds guides the amount of food eaten and is imperative for the evaluation of food quality. Once food intake is expected or commenced, the brainstem and higher centres activate the cephalic phase response and release appetite hormones in saliva.(23) These salivary hormones are postulated to play a role in metabolism; indeed, impaired oral nutrient sensing is associated with increased energy intake and a greater body mass index.(24)

Preterm infants do not have the opportunity to experience the most basic of stimuli and sensation associated with feeding: hunger, satiety, taste and smell. NICU clinicians regulate feed times, frequency and volumes of feed. Milk is delivered through a gastric tube until infants are mature enough to attempt breastfeeding bypassing the gustatory and olfactory receptors that are involved in stimulating many of the preprandial responses outlined above.

Relevant clinical trials in the NICU environment.

There are three prior studies in preterm infants in which taste may have been a variable affecting time to full enteral feeds. Rodriguez et al. (2011) reported as a secondary outcome in a randomised study of 16 extremely low birth weight (ELBW; <1000g) infants that infants receiving 2 hourly oropharyngeal colostrum for 48 hours in the first days after birth reached full enteral feeds significantly faster than the control group, receiving water instead of colostrum.(25) However, another similar study of 48 ELBW infants who received 3 hourly oropharyngeal colostrum for three days in the first days after birth, did not find any difference

in time to full enteral feeds between the intervention and control groups.(26) Both studies provided oropharyngeal colostrum for only a few days with the primary outcome being immunological effects. Neither of the studies reported if the colostrum was given in combination with tube feeds.

Another study investigated the effect of 14 days of a sweetened pacifier versus a plain pacifier on weight gain in infants born less than 34 weeks' PMA with a birth weight of more than 1250g.(27) There were no statistically significant differences between groups.

A pilot trial, preceding this study, demonstrated that smell and taste with every tube feed reduced the time to full enteral feeds in very low birthweight (VLBW, <1500g) infants. Infants who had been exposed to regular smell and taste of their milk feed also had higher weight z-scores at discharge – a crucial outcome, as higher weight z-scores are associated with better long-term neurodevelopmental outcomes.(3,28)

Following this pilot study, Bloomfield et al. included 'smell and taste with tube feeding' into their study protocol examining early feeding practices in moderate to late preterm infants and their effect on nutritional, metabolic and neurodevelopmental outcomes.(29) The same group also recently published a Cochrane Database of Systematic Reviews protocol to examine the effects of smell and taste with tube feeding.(30)

Summary and rationale

Few NICUs routinely provide infants with the smell and/or taste of their milk with tube feeds, despite the assumption that premature infants can taste and smell, and despite our own regular indulgence in smell and taste perception. It is common for smell and/or taste to be provided on an ad hoc basis, for pain relief, mouth care and/or occasionally with tube feeding. Smell and taste strongly elicit the cephalic phase response and may have the potential to improve milk tolerance, digestion and metabolism in very low birth weight infants. The few published studies that investigated the effects of taste on tube feeding expose infants only for a few days, include only late preterm infants or have small sample sizes. This trial is powered to demonstrate the effects of smell and taste of milk with every tube feed on the weight z-score at discharge. Other important outcomes include: length of stay in hospital, duration of parenteral nutrition, and late onset sepsis.

Methods and analysis

Trial design and setting

The TASTE trial is a two centre, parallel-group randomised superiority trial, including preterm infants admitted to the NICU at the Mater Mothers' Hospital (MMH) in Brisbane and the NICU at the Royal Women's Hospital (RWH) in Melbourne, both in Australia. Australian and New Zealand Clinical Trials Registry: ACTRN12617000583347: supplementary file 1.

Participant and public involvement

Feedback and discussions from families enrolled in the pilot study aided in the development of the research question and outcome measures as well as in assessing the burden of the intervention. Governance regulations did not allow for the involvement of relevant patient families in the planning of or in the recruitment to this study. Results of this study will be published on the MMH and RWH website and social media.

Eligibility criteria

Inclusion criteria: Male and female preterm infants born at less than 29 weeks' PMA and/or birth weight less than 1250 g with written informed parental/guardian consent. Consent must be obtained before 2hrly or more frequent feeds have been initiated for 24 hours.

Exclusion criteria: Congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma at birth (e.g.: anal atresia), oesophageal atresia; congenital conditions leading to impaired growth, e.g.: trisomy 21, trisomy 18, or salt wasting enteropathy.

Interventions

Treatment Group: Infants in the treatment group receive smell and taste with every tube feed by the bedside nurse:

- smell: a drop of milk on a gauze swab will be placed as close as possible to the infant's nose, without touching. The intervention will be ceased at 32 weeks' PMA in order to comply with safe sleeping recommendations.(31)
- taste: a cotton wool bud soaked in milk will be placed on the infant's tongue if the infant is less than 32 weeks' PMA. From 32 weeks' PMA, 0.2 ml of milk will be given to the infant directly on the tongue.

If the infant is asleep, the smell is given as described above. For the taste, the milk is held onto the infants' lips. If the infant shows any interest, the milk (cotton bud or syringe) is placed in the infants' mouth.

Control Group: infants receive routine care and do not have any milk in the mouth with tube feeding. Milk for tasting with nasogastric tube feeds can only be given if prescribed by a speech pathologist, usually not before 38 weeks' PMA. The control group resembles routine care and was therefore chosen as comparator.

All infants, treatment and control group, are allowed to suck feed, receive sucrose, have skin-to-skin care and other contact with their parents, smell blankets provided by parents and/or suck on pacifiers at any time if parental consent is provided. The trial ends with the removal of the nasogastric tube. Parents can decide if they want to give oral milk with tube feeds or not if an infant is discharged home on nasogastric tube feeds.

Withdrawal of consent leads to routine care currently practiced in the NICUs, that is nasogastric tube feeding without the provision of smell and taste of milk. Therefore, withdrawal of consent only in the treatment group leads to a change in the infant's care.

Bedside instructions for both allocation groups are placed at the cot side to ensure adherence to the trial protocol. Research nurses check regularly that instructions remain at the bedside and that nurses adhere to those instructions. Site investigators ensure adherence to the trial protocol. Despite regular follow up and endorsement of the trial protocol by nursing staff, treatment change may occur but will not lead to trial exclusion.

Primary outcome

- Weight z-score at discharge from hospital.

Secondary outcomes

- Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours)
- Duration of parenteral nutrition (days) total, and first episode
- Rate of late onset sepsis, diagnosed after 24 hrs of life in a symptomatic infant with positive blood culture, cerebrospinal fluid, or sterile collected urine, treated for a minimum of 5 days with antibiotics. Potential contaminants (e.g. coagulase – negative staphylococci) will be included if the infant in addition has a neutrophil left shift of ≥ 20 % and/or C – reactive protein is ≥ 10 mg/L.
- Cumulative duration of antibiotic therapy (days)
- PMA at removal of nasogastric tube
- PMA at discharge home from hospital
- Type of feeding at different time points (e.g.: type of milk given)
- Rate and severity of retinopathy of prematurity
- Rate and severity of necrotizing enterocolitis
- Rate and severity of intraventricular haemorrhage
- Rate of chronic lung disease at 36 weeks PMA
- Spontaneous intestinal perforation
- Rate of treated patent ductus arteriosus
- Anthropometric data at different time points
    - Head circumference at 28 days, 36 weeks' PMA, at discharge home
    - Length at 36 weeks' PMA, at discharge home
- Respiratory support in hours (continuous positive airway pressure or high flow nasal cannula, and endotracheal respiratory support)
- Data will be collected from infants assessed in the long term follow up program at 1 and 2 years corrected age (CA) (e.g.: anthropometric data, respiratory support, type of feeding, cerebral palsy, level within the Gross Motor Function Classification System, hearing and vision assessments, Bayley III results)
- Rate of breast feeding at 3, 6 and 12 months of CA.

Participant timeline

The schedule of enrolment, interventions and assessments is presented in table 1.

	Trial Period									
	Enrolment	Allocation	Post allocation							Closeout
Time point	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_x
Enrolment:										
Eligibility screen	x									
Informed consent	x									
Allocation		x								
Interventions:										

Smell and taste with tube feeding			●	—	●					
Routine care			●	—	●					
Assessments:										
Baseline variables	x	X								
Primary outcome					x					
Secondary outcomes				x	x	x	x	x	x	x

Table 1 Schedule of enrolment, interventions and assessments.
–t1: before allocation; t0: time of allocation/randomisation; t1: time to full enteral feeds; t2: time of full enteral feeds; t3: time of discharge; t4: 3 months CA; t5: 6 months CA; t6: 1 year CA; t7: 2 years CA; tx: 2 years CA for infants eligible for the long term follow up program, 1 year for infants not eligible for the follow up program but parents consented to be contacted for breast feeding rates, time of discharge home from hospital for all other infants.

Sample size calculation

Sample size calculation for the TASTE trial is based on detecting an improvement in weight z-score at discharge from a mean of -0.31 to -0.1 with a type I error of 5% and 90% power. Multiples are randomised together to the same study group. Therefore, twins and triplets were considered in the sample size calculation with a mother's infants from one pregnancy defined as a cluster. The pilot study had a mean cluster size of 1.08 with an intra-cluster correlation coefficient of 0.35 and a standard deviation in weight z-score at discharge of 0.58. Given these criteria, based on a two-sided generalised estimating equations (GEE) model, the required sample size was calculated to be 165 for each group.(32) This sample size is inflated and controls for clustering within multiple births.

Recruitment

The study team member will identify potential participants for the trial and approach their parents for written consent. Parents will not be approached for consent antenatally, but they may be informed about the trial. However, if parents indicate that they do want their infant to participate in the trial, a participant information and consent form (PICF – supplementary file 2) will be provided.

Participants will be actively recruited after birth and parents approached for written consent by a study team member. Potential participants for the trial will be identified from the inpatient list of the NICUs on a daily basis. Parents will be approached when they have recovered from the stress of birth and when they are able to consent. Parents will have the ability to consider participation, discuss the trial with their friends, family and local general practitioner, ask questions and decide to consent or not to the trial without any consequences to the care of their infant. Clinical care of the infant will always take priority over any research study and wherever possible, consent will be obtained by a member of the study team not directly involved in the infant's clinical care.

Randomisation

A randomisation sequence of treatment or control with variable block sizes (2-6) was generated by IH using the ralloc command of Stata 14 (College Station, TX, USA).

Randomisation is stratified by site, sex and PMA (<27 weeks' PMA and >/= 27 weeks' PMA). Each participating centre is provided with sequentially numbered, sealed, opaque, envelopes containing the assigned treatment allocation. The envelope is opened after parental consent has been given, immediately before the trial commences. One envelope is opened for each set of multiple births.

Blinding

Treatment allocation and the primary outcome are not blinded in this trial. Blinding of the treatment allocation was considered but it was concluded that it was not feasible for the intervention tested. A robust primary outcome was chosen with the aim to prevent observer bias while it is acknowledged that the potential for "treatment leakage" still exists. To mitigate this concern, we will ensure that clinical care teams, researchers, and parents/caregivers are provided education regarding the importance of maintaining the integrity of the randomisation of the trial.

The following secondary outcomes are assessed by clinicians blinded to the infant's allocated group: retinopathy of prematurity, x-ray findings required to determine the severity of necrotizing enterocolitis, intraventricular haemorrhage, presence of chronic lung disease, spontaneous intestinal perforation, respiratory support in hours, outcomes from long term follow up program from eligible infants at 1 and 2 years CA.

Data management

Data will be sourced from each participant's observation chart, clinical care team notes, medical records and verbally from parents. Each infant will be assigned a study number and data will be collected under that study number. Data will be de-identified when entered onto a paper case record form, then transferred by the data manager to an excel spread sheet and stored on a password protected computer on the MMH computer network. Each data set will be checked by the principal investigator for plausibility and data range checks are applied in the database as appropriate.

The MMH Human Research Ethics Committee reviewed the protocol and the pilot study and advised that a data monitoring committee, an interim analysis and stopping guidelines were not required for this trial.

Statistical methods

Statistical analysis will be performed by the authors Hughes and Beker with assistance of other study group members. Data will be exported from an excel spreadsheet to a statistical package for analysis (Stata; College Station, TX, USA). Data will be analysed on an intention to treat basis. All randomised infants will be included in the primary analysis, unless consent has been withdrawn. Data of deceased infants will be included in the analysis if the respective outcome is achieved.

Univariate and multivariable GEE analyses will be used for the primary outcome, weight z-scores at discharge from hospital, and other continuous secondary outcome measures. Time to full enteral feeds will be analysed using a multilevel survival analysis (mestreg command in Stata).(28) Secondary outcomes with categorical data will be analysed using a mixed effects logistic regression (melogit Stata command). Subgroup analysis will be performed based on sex and PMA for the primary outcome and selected secondary outcomes.

All outcomes will be assessed against a hypothesis of superiority.

Harms
Principal investigators / their delegates will be responsible for all safety reporting. Study infants are at high risk and rely on intensive care of their medical problems. Deaths of study infants will be reported to the approving HREC and governance department within 24 hours of knowing by the site principal investigator / delegate. This includes adjudication of the likelihood of the event being related to the involvement in this trial.

In both participating NICUs, clinical incidents are reviewed by the Patient Safety Units. Trends and concerns regarding patient safety are analysed and the results shared with the NICU's to prevent patient harm. Principal investigators will be informed by the Patient Safety Units should there be any concern in regards to the safety of the TASTE trial. The TASTE trial has no established external study monitoring committee.

Discussion

Exposure of preterm infants to the smell and taste of milk is infrequently considered by clinicians or researchers. Smell and taste of food prepares the body for food intake, digestion and metabolism and may improve important clinical outcomes of preterm infants that are challenged by sub-optimal weight gain and poor enteral milk tolerance.(28)

TASTE is the first adequately powered trial to test the effect of smell and taste in very preterm infants. Use of a placebo in the control group has proven difficult. Pavlov's experiments with dogs have demonstrated that multiple sensory inputs, not related to food intake, can elicit a cephalic phase response. The offer of normal saline or water taste on a cotton bud or via syringe is therefore not appropriate for the control group. Due to the lack of blinding a robust primary outcome (weight z-scores at discharge from hospital) was selected.

If smell and taste with tube feeding is shown to be beneficial for very preterm infants, this straight forward intervention may easily be adopted by NICUs and not only improve clinical outcomes, but also save costs and resources.

Ethics and dissemination

Research ethics
The HRECs of MML and RWH approved of the study protocol (version 3, 8th of May 2017), trial reference number HREC/16/MHS/112 and trial reference number 17/21, respectively. Both hospitals also granted governance approval.

Dissemination of results
The results of the trial will be published in a peer-reviewed journal and will be presented at national and international conferences. Authorship will be determined in line with the International Committee of Medical Journal Editors guidelines. A data sharing agreement will be in place to allow all study group members to access the final trial dataset. Access to the participant-level dataset may be granted if an appropriate data sharing agreement is arranged.

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Author contributions

FB conceived of the study. FB, IH and SEJ developed the study design and FB, HL, PGD, JM, ET and SEJ facilitated study implementation. IH provided statistical expertise in clinical trial design and together with FB planned the statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript. The primary trial sponsor is Mater Misericordiae Ltd, contact: CEO Mater Research, Governance Office, email: research.governance@mater.uq.edu.au, phone: +61 7 3163 3769. The trial sponsors have approved of the study protocol, but have no role in study design, in collection, management, analysis, and interpretation of data, in writing of the report, and the decision to submit the report for publication.

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Competing interest statement

Peter G Davis received salary support from Australia's national research funding agency. Neither the principal investigator nor the other investigators have any other financial or other competing interests for the overall trial and each study site to declare.

GLOSSARY OF ABBREVIATIONS

AE: adverse event; CA: corrected age; d: day; ELBW: extremely low birth weight; GEE: generalised estimate equations; HREC: Human Research Ethics Committee; kg: kilogram; L: litre; mg: milligram; ml: millilitre; MMH: Mater Mothers' Hospital; NICU: neonatal intensive care unit; PMA: postmenstrual age; RWH: Royal Women's Hospital; SAE: serious adverse event; VLBW: very low birth weight

Supplementary file 1

World Health Organization Trial Registration Data Set:

Data category	Information
Primary registry and trial identifying number	anzctr.org.au ACTRN12617000583347
Date of registration in primary registry	26 April, 2017
Secondary identifying numbers	Universal trial number: U1111-1192-6122
Source(s) of monetary or material support	Mater Research Institute Royal Australasian College of Physicians and Paediatricians – Queensland Branch
Primary sponsor	Mater Misericordiae Limited, South Brisbane, QLD, Australia
Secondary sponsor(s)	Royal Women's Hospital, Grattan, Victoria, Australia
Contact for public queries	Dr Friederike Beker, Neonatal Critical Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, QLD 4101, Australia Phone: +61 7 3163 1955; email: friederike.beker@mater.org.au
Contact for scientific queries	Dr Friederike Beker, contact as above
Public title	Effect of smell and taste to improve nutrition in very preterm babies
Scientific title	Smell and taste with tube feeding to improve nutrition in very preterm infants: a randomised controlled trial.
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Prematurity, growth failure, milk intolerance
Intervention(s)	smell and taste of milk (mothers' breast milk, pasteurised donor breast milk or formula) with tube feeding - with every feed for the duration of the feed <32 weeks PMA until 32 weeks PMA: cotton bud soaked in milk offered for sucking and drop of milk on cotton pad placed close to the infant's nose >32 weeks PMA until removal of nasogastric tube or discharge: 0.2 ml of milk given orally with a feeding syringe
Key inclusion and exclusion criteria	Ages eligible for study / inclusion criteria: < 29 weeks PMA and/or less than 1250 g birth weight Sexes eligible for study: both Can healthy volunteers participate? Exclusion criteria: infants with congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma after birth (e.g.: anal atresia), oesophageal atresia. 2. Congenital conditions leading to impaired growth: e.g.: trisomy 21, trisomy 18, salt wasting enteropathy.
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: open (masking not used) Primary purpose: treatment

	Phase: not applicable
Date of first enrolment	May 2017
Target sample size	330
Recruitment status	Recruiting
Primary outcome(s)	Weight z-scores at discharge home assessed by calibrated digital scales.
Key secondary outcomes	Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours), assessed by review of feeding records Duration of parenteral nutrition (days) total. Duration of antibiotics (days) total. Episodes of late onset sepsis. PMA at discharge home from hospital.

Document Title:	Research Patient Smell and taste to improve nutrition in very preterm infants: a randomized controlled trial
Unit Record No.:	
Surname:	
Given Names:	
DOB:	

Participant Information Sheet

Interventional Study - *Parent/Guardian consenting on behalf of participant*

Title	Taste and smell to improve nutrition in very preterm infants: a randomised controlled trial
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit at the Mater Mothers' Hospital

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for your baby to take part in this research project because they were born extremely premature. The research project is testing whether smelling and tasting milk before each feed improves nutrition and digestion. The only change in your baby's care will be that the baby may be given milk to taste and smell at the beginning of every tube feed.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your baby to take part in the research.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more. Before deciding whether or not the child will take part, you might want to talk about it with a relative, friend or the child's local doctor.

Participation in this research is voluntary. If you do not wish your baby to take part, they do not have to. Your baby will receive the best possible care whether or not they take part.

If you decide you want the child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you

- understand what you have read,
- consent to your baby taking part in the research project,
- consent for your baby to have the tests and treatments that are described and
- consent to the use of your baby's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Babies born extremely premature initially rely on nutrition given through the vein because their gut is immature and milk is not easily digested. When feeds are started, milk is routinely given directly into the stomach through a tube. We use a tube because preterm babies cannot yet coordinate sucking, swallowing and breathing.
We already know that preterm babies do not tolerate milk feeds very well. Many studies have tried to improve milk tolerance but there is still room to improve.

With this study we are investigating whether preterm babies tolerate milk better if they are able to smell and taste their milk before and during the time milk is given into their stomach via a tube. This is important because we know that preterm babies grow better when they are able to tolerate their milk. Regular smell and taste is not usually considered in the care of preterm babies.

We have already completed a smaller trial investigating the effects of smell and taste in preterm babies and are required to repeat it in a larger number of babies.

We hope to improve the care of preterm babies in the future. Smell and taste of milk could easily be included in routine care if it were shown to improve milk tolerance.

This research has been initiated by the study doctor, Dr Friederike Beker.

This research has been funded by Mater Research Institute.

3 What does participation in this research involve?

➤ Consent
Your baby will only participate in the study if you agree and have signed the consent form.

➤ Initial steps
We will have checked if your baby is eligible to participate in the study. Your baby will be excluded if he/she has significant problems with his/her gut from birth and/or if he/she has a medical condition that is known to affect growth.

Your baby can participate in this study if you sign the consent form.

Enrolment in this study will not affect participation in other studies.

All babies will be allocated to one of two groups by chance. One group of babies will receive routine care, the other group will receive the intervention (smell and taste their milk before each feed).

➤ Intervention

Babies in one study group will smell and taste their milk before each feed, starting after you have consented. A cotton wool pad with a drop of milk will be placed in front of their nose. In addition, a cotton wool bud soaked in milk or a small feeding syringe will be used to provide taste by touching the tongue with milk. Cotton wool buds and feeding syringes are used in routine care for the application of medication.

The control group will not smell and taste their milk with tube feeding as is currently the common practice in the nursery. The intervention will continue until the nasogastric tube is removed. All babies in the treatment or control group may have breast feeds, dummies, sucrose for pain relief, cuddles with parents and/or parents scent at any time at the discretion of the treating clinical team.

Your baby will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same and to reduce bias it is important that each participant is put into a group by chance (random).

This research project has been designed in this way to make sure the researchers interpret the results in a fair and appropriate way and avoid study doctors or participants jumping to conclusions.

There are no additional costs associated with participation in this research project, nor will you or the participant be paid. All medical care required as part of the research project will be provided to your baby free of charge.

4 What does my baby have to do?

Your baby will be randomised to either the treatment or intervention group. According to randomisation, your baby will receive routine care or will taste and smell the milk before each tube feed. Data will be recorded about your baby's progress but there are no additional commitments required for your baby.

5 Other relevant information about the research project

A total of 330 preterm babies will take part in this research project, 165 in each group. Babies will be recruited at the Neonatal Critical Care Unit at the Mater Mothers' Hospital and at the Neonatal Intensive and Special Care at the Royal Women's Hospital, Melbourne. This project is a follow up from the previous pilot study called 'Smell and taste to improve nutrition in preterm infants: a randomised controlled pilot trial' and involves researchers from the Mater Mothers' and Royal Women's Hospitals and from the Mater Research Institute.

6 Does my baby have to take part in this research project?

Participation in any research project is voluntary. If you do not wish your baby to take part, they do not have to. If you decide that they may take part and later change your mind, you are free to withdraw your baby from the project at any stage.

If you do decide that your baby can take part, you will need to sign this Parent Information and Consent Form and you will be given a copy to keep.

Your decision that your baby may or may not take part or that they may take part and then be withdrawn will not affect their routine treatment, relationship with those treating them or their relationship with The Mater Mothers' Hospital.

7 What are the alternatives to participation?

Your baby does not have to take part in this research project to receive full treatment at this hospital.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the child will receive any benefits from this research. However, possible benefits may include better tolerance of milk feeds and/or improved growth.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects, however, we are not aware of any issues associated with smell and taste of milk. In case your baby experiences any discomfort or side effects, or you are worried about them, talk with any of the staff. We will take your concerns seriously and will manage any discomfort and concerns related to the study.

If you or your baby becomes upset or distressed as a result of participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who is not members of the research project team. This counselling will be provided free of charge.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want your baby to continue in the research project. If you decide to withdraw your baby, their study doctor will make arrangements for their regular health care to continue.

11 Can the child have other treatments during this research project?

Your baby can have all other treatment during the research project. No restrictions are necessary.

12 What if I withdraw the child from this research project?

If you decide to withdraw your baby from the project, please notify a member of the research team before you withdraw them. This notice will allow that person or the research supervisor to discuss further any health risks or special requirements linked to withdrawing.

If you do withdraw your baby from the study, personal information already collected will be retained but no further data will be collected. This is to ensure that the results of the research project can be measured properly and comply with law. If you do not want the study team to use already collected data, you must tell them before your baby joins the research project.

You also have the option to withdraw your baby from the study procedure only and allow the research team to continue with data collection past the time point of withdrawal from the study procedure.

Mater Research

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects.

14 What happens when the research project ends?

Babies born at less than 28 weeks gestation or below 1000g are routinely offered developmental follow up at 1 and 2 years of age. We would like to collect data from those follow up assessments.
If you give us permission, we will contact you at ~ 1 year corrected age to ask how your baby is doing and about how long you breast fed.

Part 2 How is the research project being conducted?

15 What will happen to information about the child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your baby for the research project. Any information obtained in connection with this research project that can identify your baby will remain confidential.

Data will be stored de-identified under a study number on a password locked work computer. A list linking the study number to your baby's personal details will be kept in a locked cupboard in the Research Office. Your baby's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your baby may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your baby's participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums (e.g., conferences, journal articles, teaching presentations). In any publication and/or presentation, information will be provided in such a way that your baby cannot be identified, except with your permission. Confidentiality will be maintained as results will only be published in a de-identified manner.

Information about your baby's participation in this research project may be recorded in their health records.

In accordance with relevant Australian and Queensland privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member whose name appears at the end of this document if you would like to access your baby's information.

Any information obtained for the purpose of this research project that can identify your baby will be treated as confidential and securely stored. It will be disclosed only with your permission or as required by law.

16 Complaints and Compensation

If your baby suffers as a result of this research project, appropriate medical treatment for your baby will be arranged. If your baby is eligible for Medicare, they can receive any medical treatment required free of charge as a public patient in any Australian public hospital.

17 Who is organising and funding the research?

This research project is being organised and funded by the Mater Research Institute.

No member of the research team will receive a personal financial benefit from your baby's involvement in this research project (other than their ordinary wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Mater Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 07 3163 1918 or any of the following people:

Mater Research Nurse	Phone: 07 3163 8543
Human Research Ethics Committee	Phone: 07 3163 1585

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.
A copy of the information sheet and consent form is for you to keep.

Consent Form – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital, South Brisbane

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my baby's doctors, other health professionals or hospitals outside this hospital to release information to the study team concerning my baby's disease and treatment for the purpose of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

☐ I freely agree to my baby's participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

☐ I agree to the collection of the results of my baby's 1 and 2 year follow-up developmental assessment (if performed)

☐ I agree to be contacted by a research nurse when my baby is 1 year old about the duration of breast feeding. I can change my decision any time.

I understand that I will be given a signed copy of this document to keep.

Name of Baby (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Name of Witness* to Parent/Guardian Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Form for Withdrawal of Participation – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital

Declaration by Parent/Guardian

I wish to withdraw the child from participation in the above research project and understand that such withdrawal will not affect their routine treatment, relationships with those treating them or the relationship with *the Mater Mothers' Hospital.*

I agree to data collection to continue past withdrawal from the study procedure: ☐ yes; ☐ no

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Description of circumstances:

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name	1

		of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1, sup 1
Protocol version	#3	Date and version identifier	1+9
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and	7

		statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	N/A

emergency unblinding		permissible, and procedure for revealing a participant's allocated intervention during the trial	
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1+9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	N/A

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public,	1+9

		and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7, sup 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

The effect of smell and taste of milk during tube feeding of preterm infants (the TASTE trial): a protocol for a randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027805.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Jun-2019
Complete List of Authors:	Beker, Friederike; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Macey, Judith; University of Queensland, Mater Research Institute Liley, Helen; University of Queensland, Mater Research Institute; Mater Mothers' Hospital, Neonatal Critical Care Unit Hughes, Ian; Gold Coast University Hospital Davis, Peter; The Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research Twitchell, Emily; Murdoch Childrens Research Institute, Clinical Sciences Research Jacobs, Susan; Royal Women's Hospital, Neonatal Intensive Care Unit and Newborn Research; Murdoch Childrens Research Institute, Clinical Sciences Research
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care, Nutrition and metabolism
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NUTRITION & DIETETICS, Nutritional support < GASTROENTEROLOGY

The effect of smell and taste of milk during tube feeding of preterm infants (the TASTE trial): a protocol for a randomised controlled trial.

Friederike Beker[1,2], Judith Macey[1], Helen Liley[1,2], Ian Hughes[3], Peter G Davis[4,5], Emily Twitchell[5], Susan Jacobs[4,5].

[1] Mater Research Institute, University of Queensland, South Brisbane, Australia; [2] Neonatal Intensive Care Unit, Mater Mothers' Hospital, South Brisbane, Australia; [3] Gold Coast University Hospital, Southport, Australia; [4] Neonatal Intensive Care Unit and Newborn Research Centre, Royal Women's Hospital, Parkville, Australia; [5] Clinical Sciences Research, Murdoch Children's Research Institute, Parkville, Australia.

Corresponding author: Friederike Beker, Neonatal Intensive Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, Queensland 4101, Australia; email: friederike.beker@mater.org.au; phone: +61 7 3163 1955

Word count: 3809

Key words: neonatology, paediatrics, nutrition, tube feeding, growth

Abstract

Introduction Smell and taste of milk are not generally considered when tube feeding preterm infants. Preterm infants have rapid growth, particularly of the brain, and high caloric needs. Enteral feeding is often poorly tolerated which may lead to growth failure and long-term neurodevelopmental impairment. Smell and taste are strong stimulators of digestion and metabolism. We hypothesise that regular smell and taste during tube feeding will improve weight z-scores of very preterm infants at discharge from hospital.

Methods and analysis TASTE is a randomised, un-blinded two-centre trial. Infants born at <29 weeks' gestation and/or <1250g at birth and admitted to a participating neonatal intensive care unit are eligible. Randomisation occurs before infants receive 2hrly feeds for 24 hours. Infants are randomised to either smell and taste of milk with each tube feed or tube feeding without the provision of smell and taste. The primary outcome is weight z-score at discharge. Secondary outcomes include: days to full enteral feeds, duration of parenteral nutrition, rate of late-onset sepsis, post menstrual age at removal of nasogastric tube and at discharge from hospital, anthropometric data, and neurodevelopmental outcomes at two years of corrected age.

Ethics and dissemination Human Research Ethics Committees of Mater Misericordiae Ltd (trial reference number: HREC/16/MHS/112) and the Royal Women's Hospital (trial reference number: 17/21) last approved the trial protocol (Version 4.2; Date December 18th, 2018) and recruitment commenced in May 2017 and November 2017, respectively. The trial results will be published in a peer reviewed journal and will be presented at national and international conferences.

Trial registration number Australian and New Zealand Clinical Trials Registry: ACTRN12617000583347: supplementary file 1.

Strength and limitations of this trial

- This trial is the first adequately powered randomised trial to investigate the effects of smell and taste during tube feeding of very preterm infants.
- Blinding of the allocated intervention is not feasible, therefore an objective criterion for the primary outcome (weight z-score at discharge) was specified.
- Effects of other smell or taste experiences, for example encountered during skin to skin time, with reflux or due to the tastes of varying milk types are not considered and occur in both study groups.
- Smelling and tasting of milk is an uncomplicated and potentially cost-effective intervention that may have a number of beneficial health effects such as improved weight gain and feed tolerance as well as a reduction in length of hospital stay.

Introduction

Background and rationale

Close to 7000 infants are born before term and admitted to neonatal intensive care units (NICUs) across Australia and New Zealand each year.(1) Preterm infants have an impaired ability to breathe, suck and swallow in a coordinated fashion. This immaturity presents a significant challenge to the provision of effective nutrition, commonly leading to postnatal growth failure.(2) Brain growth in the last four to eight weeks of gestation is extremely rapid and is crucial for later development. Malnutrition during a vulnerable phase of brain development leads to a reduced number of neurons and later behaviour, learning and memory problems. In preterm infants, this extremely rapid phase of brain growth occurs *ex utero* at a time when providing adequate nutrition is challenging. Thus, optimising postnatal growth may result in improved neurodevelopmental outcomes.(3,4)

Taste and smell in the NICU

Pleasant odours and tastes, such as those encountered with a good meal or a familiar person, have an enormous influence on our own daily well-being. Despite our own understanding of the role of taste and smell in our lives, preterm infants are usually only exposed to the smell of the mother's skin or breast milk once the infant is well enough to be removed from the incubator for skin-to-skin care and breast feeding. The frequency and duration of such skin-to-skin care is dependent upon the philosophy of the NICU and individual staff.(5) The infant's most common smell experience is often restricted to the odours of the direct environment, commonly excrement and antiseptics. Taste experiences may be dominated by rubber and plastic from feeding and breathing tubes in the mouth or associated with discomfort and pain, when breastmilk or sucrose is given for pain relief.(6,7) Thus, preterm infants are not only deprived of the pleasures of smell and taste but it is also possible that placement of milk feeds directly into the stomach via a feeding tube without any food anticipation may impact on metabolism and early nutritional learning.

Food anticipation and the cephalic phase response

Anticipation of food activates the digestive system. Pavlov famously explored and described this phenomenon over a hundred years ago.(8) Sham feeding, the mere taste of food in the oral cavity of dogs, led to the production of gastric secretions. Pavlov also confirmed that the sight of food or even unrelated signals such as the sound of a bell could elicit the same

strong response, as long as the dog was conditioned and knew that the bell was related to food intake. In an experiment analogous to the gastric feeding of preterm infants, Pavlov also placed bread into the stomach of his dogs through a tube, without the dog being aware. The bread remained undigested in the dogs' stomachs for up to one hour. Furthermore, Pavlov stated that a food ingested by a dog only acted as a stimulus when it "suited the dog's taste". He concluded that the response of the stomach to the anticipation of food depended on the presence of appetite.(8,9) This activation of the digestive system by anticipation of food has been named the 'cephalic response'.(10,11) Decades of ongoing research have revealed that the cephalic response plays an even more complex role in nutrition, from early nutritional learning to improved nutrient absorption, increased stomach and gut motility, anticipatory secretion of insulin with tighter blood glucose control, and the release of appetite, digestive and metabolic hormones such as leptin, ghrelin, insulin and gastrin.(12,13)

Smell and taste in preterm infants

Preterm infants are believed to have flavour perception. Functional taste receptors are present from 18 weeks' postmenstrual age (PMA) and flavour perception is established around 24 weeks' PMA. Changes in tissue oxygenation by near-infrared spectroscopy have been detected in term and preterm infants >32 weeks' PMA in response to odours, with different responses occurring to odours rated as pleasant or unpleasant.(14,15)

Amniotic fluid and breast milk have flavours that reflect the foods, spices, and beverages consumed by the mother.(16,17) Infants exposed to those flavours during late pregnancy and early infancy exhibit food preference to such flavours, some persisting into adulthood.(18) It is well known that toddlers prefer the flavour composition they have been exposed to *in utero* and during breast feeding (the mother's diet) as infants.(19) Similarly, exposure to alcohol in late pregnancy makes alcohol more palatable in later life and even increases intake.(20,21) It is also suspected that intra-uterine and postnatal exposure to fructose increases the rate of obesity later by altering feeding behaviour and appetite control as well as neuroendocrine function.(22)

Early priming of the olfactory and gustatory systems is critical, as the ability to 'taste' chemical compounds guides the amount of food eaten and is imperative for the evaluation of food quality. Once food intake is expected or commenced, the brainstem and higher centres activate the cephalic phase response and release appetite hormones in saliva.(23) These salivary hormones are postulated to play a role in metabolism; indeed, impaired oral nutrient sensing is associated with increased energy intake and a greater body mass index.(24)

Preterm infants do not have the opportunity to experience the most basic of stimuli and sensation associated with feeding: hunger, satiety, taste and smell. NICU clinicians regulate feed times, frequency and volumes of feed. Milk is delivered through a gastric tube until infants are mature enough to attempt breastfeeding bypassing the gustatory and olfactory receptors that are involved in stimulating many of the preprandial responses outlined above.

Relevant clinical trials in the NICU environment.

There are three prior studies in preterm infants in which taste may have been a variable affecting time to full enteral feeds. Rodriguez et al. (2011) reported as a secondary outcome in a randomised study of 16 extremely low birth weight (ELBW; <1000g) infants that infants receiving 2 hourly oropharyngeal colostrum for 48 hours in the first days after birth reached

full enteral feeds significantly faster than the control group, receiving water instead of colostrum.(25) However, another similar study of 48 ELBW infants who received 3 hourly oropharyngeal colostrum for three days in the first days after birth, did not find any difference in time to full enteral feeds between the intervention and control groups.(26) Both studies provided oropharyngeal colostrum for only a few days with the primary outcome being immunological effects. Neither of the studies reported if the colostrum was given in combination with tube feeds.

Another study investigated the effect of 14 days of a sweetened pacifier versus a plain pacifier on weight gain in infants born less than 34 weeks' PMA with a birth weight of more than 1250g.(27) There were no statistically significant differences between groups.

A pilot trial, preceding this study, demonstrated that smell and taste with every tube feed reduced the time to full enteral feeds in very low birthweight (VLBW, <1500g) infants. Infants who had been exposed to regular smell and taste of their milk feed also had higher weight z-scores at discharge – a crucial outcome, as higher weight z-scores are associated with better long-term neurodevelopmental outcomes.(3,28)

Following this pilot study, Bloomfield et al. included 'smell and taste with tube feeding' into their study protocol examining early feeding practices in moderate to late preterm infants and their effect on nutritional, metabolic and neurodevelopmental outcomes.(29) The same group also recently published a Cochrane Database of Systematic Reviews protocol to examine the effects of smell and taste with tube feeding.(30)

Summary and rationale

Few NICUs routinely provide infants with the smell and/or taste of their milk with tube feeds, despite the assumption that premature infants can taste and smell, and despite our own regular indulgence in smell and taste perception. It is common for smell and/or taste to be provided on an ad hoc basis, for pain relief, mouth care and/or occasionally with tube feeding. Smell and taste strongly elicit the cephalic phase response and may have the potential to improve milk tolerance, digestion and metabolism in very low birth weight infants. The few published studies that investigated the effects of taste on tube feeding expose infants only for a few days, include only late preterm infants or have small sample sizes. This trial is powered to demonstrate the effects of smell and taste of milk with every tube feed on the weight z-score at discharge. Other important outcomes include: length of stay in hospital, duration of parenteral nutrition, and late onset sepsis.

Methods and analysis

Trial design and setting

The TASTE trial is a two centre, parallel-group randomised superiority trial, including preterm infants admitted to the NICU at the Mater Mothers' Hospital (MMH) in Brisbane and the NICU at the Royal Women's Hospital (RWH) in Melbourne, both in Australia. The TASTE trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12617000583347: supplementary file 1).

Participant and public involvement

Feedback and discussions from families enrolled in the pilot study aided in the development of the research question and outcome measures as well as in assessing the burden of the

intervention. Governance regulations did not allow for the involvement of relevant patient families in the planning of or in the recruitment to this study. Results of this study will be published on the MMH and RWH website and social media.

Eligibility criteria

Inclusion criteria: Male and female preterm infants born at less than 29 weeks' PMA and/or birth weight less than 1250 g with written informed parental/guardian consent. Consent must be obtained before 2hrly or more frequent feeds have been initiated for 24 hours.

Exclusion criteria: Congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma at birth (e.g.: anal atresia), oesophageal atresia; congenital conditions leading to impaired growth, e.g.: trisomy 21, trisomy 18, or salt wasting enteropathy.

Interventions

Treatment Group: Infants in the treatment group receive smell and taste with every tube feed by the bedside nurse:

- smell: a drop of milk on a gauze swab will be placed as close as possible to the infant's nose, without touching. The intervention will be ceased at 32 weeks' PMA in order to comply with safe sleeping recommendations.(31)
- taste: a cotton wool bud soaked in milk will be placed on the infant's tongue if the infant is less than 32 weeks' PMA. From 32 weeks' PMA, 0.2 ml of milk will be given to the infant directly on the tongue.

If the infant is asleep, the smell is given as described above. For the taste, the milk is held onto the infants' lips. If the infant shows any interest, the milk (cotton bud or syringe) is placed in the infants' mouth.

Control Group: infants receive routine care and do not have any milk in the mouth with tube feeding. Milk for tasting with nasogastric tube feeds can only be given if prescribed by a speech pathologist, usually not before 38 weeks' PMA. The control group resembles routine care and was therefore chosen as comparator.

All infants, treatment and control group, are allowed to suck feed, receive sucrose, have skin-to-skin care and other contact with their parents, smell blankets provided by parents and/or suck on pacifiers at any time if parental consent is provided. The trial ends with the removal of the nasogastric tube. Parents can decide if they want to give oral milk with tube feeds or not if an infant is discharged home on nasogastric tube feeds.

Withdrawal of consent leads to routine care currently practiced in the NICUs, that is nasogastric tube feeding without the provision of smell and taste of milk. Therefore, withdrawal of consent only in the treatment group leads to a change in the infant's care.

Bedside instructions for both allocation groups are placed at the cot side to ensure adherence to the trial protocol. Research nurses check regularly that instructions remain at the bedside and that nurses adhere to those instructions. Site investigators ensure adherence to the trial protocol. Despite regular follow up and endorsement of the trial protocol by nursing staff, treatment change may occur but will not lead to trial exclusion.

Primary outcome

- Weight z-score at discharge from hospital.

Secondary outcomes

- Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours)
- Duration of parenteral nutrition (days) total, and first episode
- Rate of late onset sepsis, diagnosed after 24 hrs of life in a symptomatic infant with positive blood culture, cerebrospinal fluid, or sterile collected urine, treated for a minimum of 5 days with antibiotics. Potential contaminants (e.g. coagulase – negative staphylococci) will be included if the infant in addition has a neutrophil left shift of ≥ 20 % and/or C – reactive protein is ≥ 10 mg/L.
- Cumulative duration of antibiotic therapy (days)
- PMA at removal of nasogastric tube
- PMA at discharge home from hospital
- Type of feeding at different time points (e.g.: type of milk given)
- Rate and severity of retinopathy of prematurity
- Rate and severity of necrotizing enterocolitis
- Rate and severity of intraventricular haemorrhage
- Rate of chronic lung disease at 36 weeks PMA
- Spontaneous intestinal perforation
- Rate of treated patent ductus arteriosus
- Anthropometric data at different time points
    - Head circumference at 28 days, 36 weeks' PMA, at discharge home
    - Length at 36 weeks' PMA, at discharge home
- Respiratory support in hours (continuous positive airway pressure or high flow nasal cannula, and endotracheal respiratory support)
- Data will be collected from infants assessed in the long term follow up program at 1 and 2 years corrected age (CA) (e.g.: anthropometric data, respiratory support, type of feeding, cerebral palsy, level within the Gross Motor Function Classification System, hearing and vision assessments, Bayley III results)
- Rate of breast feeding at 3, 6 and 12 months of CA.

Participant timeline

The schedule of enrolment, interventions and assessments is presented in table 1.

	Trial Period									
	Enrolment	Allocation	Post allocation							Closeout
Time point	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_x
Enrolment:										
Eligibility screen	x									
Informed consent	x									
Allocation		x								

Interventions:										
Smell and taste with tube feeding			●	—	●					
Routine care			●	—	●					
Assessments:										
Baseline variables	x	X								
Primary outcome					x					
Secondary outcomes				x	x	x	x	x	x	x

Table 1 Schedule of enrolment, interventions and assessments.
–t1: before allocation; t0: time of allocation/randomisation; t1: time to full enteral feeds; t2: time of full enteral feeds; t3: time of discharge; t4: 3 months CA; t5: 6 months CA; t6: 1 year CA; t7: 2 years CA; tx: 2 years CA for infants eligible for the long term follow up program, 1 year for infants not eligible for the follow up program but parents consented to be contacted for breast feeding rates, time of discharge home from hospital for all other infants.

Sample size calculation

Sample size calculation for the TASTE trial is based on detecting an improvement in weight z-score at discharge from a mean of -0.31 to -0.1 with a type I error of 5% and 90% power. Multiples are randomised together to the same study group. Therefore, twins and triplets were considered in the sample size calculation with a mother's infants from one pregnancy defined as a cluster. The pilot study had a mean cluster size of 1.08 with an intra-cluster correlation coefficient of 0.35 and a standard deviation in weight z-score at discharge of 0.58. Given these criteria, based on a two-sided generalised estimating equations (GEE) model, the required sample size was calculated to be 165 for each group.(32) This sample size is inflated and controls for clustering within multiple births.

Recruitment

The study team member will identify potential participants for the trial and approach their parents for written consent. Parents will not be approached for consent antenatally, but they may be informed about the trial. However, if parents indicate that they do want their infant to participate in the trial, a participant information and consent form (PICF – supplementary file 2) will be provided.

Participants will be actively recruited after birth and parents approached for written consent by a study team member. Potential participants for the trial will be identified from the inpatient list of the NICUs on a daily basis. Parents will be approached when they have recovered from the stress of birth and when they are able to consent. Parents will have the ability to consider participation, discuss the trial with their friends, family and local general practitioner, ask questions and decide to consent or not to the trial without any consequences to the care of their infant. Clinical care of the infant will always take priority over any research study and wherever possible, consent will be obtained by a member of the study team not directly involved in the infant's clinical care.

Randomisation
A randomisation sequence of treatment or control with variable block sizes (2-6) was generated by IH using the ralloc command of Stata 14 (College Station, TX, USA). Randomisation is stratified by site, sex and PMA (<27 weeks' PMA and >/= 27 weeks' PMA). Each participating centre is provided with sequentially numbered, sealed, opaque, envelopes containing the assigned treatment allocation. The envelope is opened after parental consent has been given, immediately before the trial commences. One envelope is opened for each set of multiple births.

Blinding
Treatment allocation and the primary outcome are not blinded in this trial. Blinding of the treatment allocation was considered but it was concluded that it was not feasible for the intervention tested. A robust primary outcome was chosen with the aim to prevent observer bias while it is acknowledged that the potential for "treatment leakage" still exists. To mitigate this concern, we will ensure that clinical care teams, researchers, and parents/caregivers are provided education regarding the importance of maintaining the integrity of the randomisation of the trial.

The following secondary outcomes are assessed by clinicians blinded to the infant's allocated group: retinopathy of prematurity, x-ray findings required to determine the severity of necrotizing enterocolitis, intraventricular haemorrhage, presence of chronic lung disease, spontaneous intestinal perforation, respiratory support in hours, outcomes from long term follow up program from eligible infants at 1 and 2 years CA.

Data management
Data will be sourced from each participant's observation chart, clinical care team notes, medical records and verbally from parents. Each infant will be assigned a study number and data will be collected under that study number. Data will be de-identified when entered onto a paper case record form, then transferred by the data manager to an excel spread sheet and stored on a password protected computer on the MMH computer network. Each data set will be checked by the principal investigator for plausibility and data range checks are applied in the database as appropriate.

The MMH Human Research Ethics Committee reviewed the protocol and the pilot study and advised that a data monitoring committee, an interim analysis and stopping guidelines were not required for this trial.

Statistical methods
Statistical analysis will be performed by the authors Hughes and Beker with assistance of other study group members. Data will be exported from an excel spreadsheet to a statistical package for analysis (Stata; College Station, TX, USA). Data will be analysed on an intention to treat basis. All randomised infants will be included in the primary analysis, unless consent has been withdrawn. Data of deceased infants will be included in the analysis if the respective outcome is achieved.

Univariate and multivariable GEE analyses will be used for the primary outcome, weight z-scores at discharge from hospital, and other continuous secondary outcome measures. Time to full enteral feeds will be analysed using a multilevel survival analysis (mestreg command in Stata).(28) Secondary outcomes with categorical data will be analysed using a mixed

effects logistic regression (melogit Stata command). Subgroup analysis will be performed based on sex and PMA for the primary outcome and selected secondary outcomes.

All outcomes will be assessed against a hypothesis of superiority.

Harms

Principal investigators / their delegates will be responsible for all safety reporting. Study infants are at high risk and rely on intensive care of their medical problems. Deaths of study infants will be reported to the approving HREC and governance department within 24 hours of knowing by the site principal investigator / delegate. This includes adjudication of the likelihood of the event being related to the involvement in this trial.

In both participating NICUs, clinical incidents are reviewed by the Patient Safety Units. Trends and concerns regarding patient safety are analysed and the results shared with the NICU's to prevent patient harm. Principal investigators will be informed by the Patient Safety Units should there be any concern in regards to the safety of the TASTE trial. The TASTE trial has no established external study monitoring committee.

Discussion

Exposure of preterm infants to the smell and taste of milk is infrequently considered by clinicians or researchers. Smell and taste of food prepares the body for food intake, digestion and metabolism and may improve important clinical outcomes of preterm infants that are challenged by sub-optimal weight gain and poor enteral milk tolerance.(28)

TASTE is the first adequately powered trial to test the effect of smell and taste in very preterm infants. Use of a placebo in the control group has proven difficult. Pavlov's experiments with dogs have demonstrated that multiple sensory inputs, not related to food intake, can elicit a cephalic phase response. The offer of normal saline or water taste on a cotton bud or via syringe is therefore not appropriate for the control group. Due to the lack of blinding a robust primary outcome (weight z-scores at discharge from hospital) was selected.

It is widely accepted that weight gain is based on a balance of calories provided paired with the metabolic needs of the infants. Regular smell and taste with feeding may play an additional role in nutrition by modifying digestion and absorption as well as influence early nutritional learning in the form of appetite and satiety regulation. The selection of weight z-scores at discharge as the primary outcome measure for this study is based on that assumption supported by the results of our pilot trial.(28) Weight at discharge also seemed more relevant than short term nutritional outcomes as a relationship between weight at discharge and long term neurodevelopmental outcomes has been reported.(2,3)

Full enteral feeds are reported as secondary outcome at 120 ml/kg/d instead of 150 or 160 ml/kg/d as recommended by the COMMENT (Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials) group. Their core data set was developed based on a previous proposal by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition.(33) A rationale for choosing 120 ml/kg/d over higher amounts of milk may be the fluid restriction of infants for non - nutrition related reasons to below 150 ml/kg/d (less likely below 120ml/kg/d) so the time to reach 150 ml/kg/d may be delayed until fluid restriction is ceased.

If smell and taste with tube feeding is shown to be beneficial for very preterm infants, this straight forward intervention may easily be adopted by NICUs and not only improve clinical outcomes, but also save costs and resources.

Ethics and dissemination

Research ethics

The HRECs of MML and RWH approved of the study protocol (version 3, 8th of May 2017), trial reference number HREC/16/MHS/112 and trial reference number 17/21, respectively. Both hospitals also granted governance approval.

Dissemination of results

The results of the trial will be published in a peer-reviewed journal and will be presented at national and international conferences. Authorship will be determined in line with the International Committee of Medical Journal Editors guidelines. A data sharing agreement will be in place to allow all study group members to access the final trial dataset. Access to the participant-level dataset may be granted if an appropriate data sharing agreement is arranged.

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Author contributions

FB conceived of the study. FB, IH and SEJ developed the study design and FB, HL, PGD, JM, ET and SEJ facilitated study implementation. IH provided statistical expertise in clinical

trial design and together with FB planned the statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript. The primary trial sponsor is Mater Misericordiae Ltd, contact: CEO Mater Research, Governance Office, email: research.governance@mater.uq.edu.au, phone: +61 7 3163 3769. The trial sponsors have approved of the study protocol, but have no role in study design, in collection, management, analysis, and interpretation of data, in writing of the report, and the decision to submit the report for publication.

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Competing interest statement

Peter G Davis received salary support from Australia's national research funding agency. Neither the principal investigator nor the other investigators have any other financial or other competing interests for the overall trial and each study site to declare.

GLOSSARY OF ABBREVIATIONS

AE: adverse event; CA: corrected age; d: day; ELBW: extremely low birth weight; GEE: generalised estimate equations; HREC: Human Research Ethics Committee; kg: kilogram; L: litre; mg: milligram; ml: millilitre; MMH: Mater Mothers' Hospital; NICU: neonatal intensive care unit; PMA: postmenstrual age; RWH: Royal Women's Hospital; SAE: serious adverse event; VLBW: very low birth weight

Supplementary file 1

World Health Organization Trial Registration Data Set:

Data category	Information
Primary registry and trial identifying number	anzctr.org.au ACTRN12617000583347
Date of registration in primary registry	26 April, 2017
Secondary identifying numbers	Universal trial number: U1111-1192-6122
Source(s) of monetary or material support	Mater Research Institute Royal Australasian College of Physicians and Paediatricians – Queensland Branch
Primary sponsor	Mater Misericordiae Limited, South Brisbane, QLD, Australia
Secondary sponsor(s)	Royal Women's Hospital, Grattan, Victoria, Australia
Contact for public queries	Dr Friederike Beker, Neonatal Critical Care Unit, Mater Mothers' Hospital, Raymond Terrace, South Brisbane, QLD 4101, Australia Phone: +61 7 3163 1955; email: friederike.beker@mater.org.au
Contact for scientific queries	Dr Friederike Beker, contact as above
Public title	Effect of smell and taste to improve nutrition in very preterm babies
Scientific title	Smell and taste with tube feeding to improve nutrition in very preterm infants: a randomised controlled trial.
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Prematurity, growth failure, milk intolerance
Intervention(s)	smell and taste of milk (mothers' breast milk, pasteurised donor breast milk or formula) with tube feeding - with every feed for the duration of the feed <32 weeks PMA until 32 weeks PMA: cotton bud soaked in milk offered for sucking and drop of milk on cotton pad placed close to the infant's nose >32 weeks PMA until removal of nasogastric tube or discharge: 0.2 ml of milk given orally with a feeding syringe
Key inclusion and exclusion criteria	Ages eligible for study / inclusion criteria: < 29 weeks PMA and/or less than 1250 g birth weight Sexes eligible for study: both Can healthy volunteers participate? Exclusion criteria: infants with congenital conditions associated with the digestive system requiring surgery shortly after birth, e.g.: gastroschisis, any malformation requiring a stoma after birth (e.g.: anal atresia), oesophageal atresia. 2. Congenital conditions leading to impaired growth: e.g.: trisomy 21, trisomy 18, salt wasting enteropathy.
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: open (masking not used) Primary purpose: treatment

	Phase: not applicable
Date of first enrolment	May 2017
Target sample size	330
Recruitment status	Recruiting
Primary outcome(s)	Weight z-scores at discharge home assessed by calibrated digital scales.
Key secondary outcomes	Time (days) to full enteral feeds (120 ml/kg/d for at least 24 hours), assessed by review of feeding records Duration of parenteral nutrition (days) total. Duration of antibiotics (days) total. Episodes of late onset sepsis. PMA at discharge home from hospital.

Document Title:	Research Patient Smell and taste to improve nutrition in very preterm infants: a randomized controlled trial
Unit Record No.:	
Surname:	
Given Names:	
DOB:	

Participant Information Sheet

Interventional Study - *Parent/Guardian consenting on behalf of participant*

Title	Taste and smell to improve nutrition in very preterm infants: a randomised controlled trial
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit at the Mater Mothers' Hospital

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for your baby to take part in this research project because they were born extremely premature. The research project is testing whether smelling and tasting milk before each feed improves nutrition and digestion. The only change in your baby's care will be that the baby may be given milk to taste and smell at the beginning of every tube feed.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your baby to take part in the research.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more. Before deciding whether or not the child will take part, you might want to talk about it with a relative, friend or the child's local doctor.

Participation in this research is voluntary. If you do not wish your baby to take part, they do not have to. Your baby will receive the best possible care whether or not they take part.

If you decide you want the child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you

- understand what you have read,
- consent to your baby taking part in the research project,
- consent for your baby to have the tests and treatments that are described and
- consent to the use of your baby's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Babies born extremely premature initially rely on nutrition given through the vein because their gut is immature and milk is not easily digested. When feeds are started, milk is routinely given directly into the stomach through a tube. We use a tube because preterm babies cannot yet coordinate sucking, swallowing and breathing.
We already know that preterm babies do not tolerate milk feeds very well. Many studies have tried to improve milk tolerance but there is still room to improve.

With this study we are investigating whether preterm babies tolerate milk better if they are able to smell and taste their milk before and during the time milk is given into their stomach via a tube. This is important because we know that preterm babies grow better when they are able to tolerate their milk. Regular smell and taste is not usually considered in the care of preterm babies.

We have already completed a smaller trial investigating the effects of smell and taste in preterm babies and are required to repeat it in a larger number of babies.

We hope to improve the care of preterm babies in the future. Smell and taste of milk could easily be included in routine care if it were shown to improve milk tolerance.

This research has been initiated by the study doctor, Dr Friederike Beker.

This research has been funded by Mater Research Institute.

3 What does participation in this research involve?

➤ Consent
Your baby will only participate in the study if you agree and have signed the consent form.

➤ Initial steps
We will have checked if your baby is eligible to participate in the study. Your baby will be excluded if he/she has significant problems with his/her gut from birth and/or if he/she has a medical condition that is known to affect growth.

Your baby can participate in this study if you sign the consent form.

Enrolment in this study will not affect participation in other studies.

All babies will be allocated to one of two groups by chance. One group of babies will receive routine care, the other group will receive the intervention (smell and taste their milk before each feed).

➤ Intervention

Babies in one study group will smell and taste their milk before each feed, starting after you have consented. A cotton wool pad with a drop of milk will be placed in front of their nose. In addition, a cotton wool bud soaked in milk or a small feeding syringe will be used to provide taste by touching the tongue with milk. Cotton wool buds and feeding syringes are used in routine care for the application of medication.

The control group will not smell and taste their milk with tube feeding as is currently the common practice in the nursery. The intervention will continue until the nasogastric tube is removed. All babies in the treatment or control group may have breast feeds, dummies, sucrose for pain relief, cuddles with parents and/or parents scent at any time at the discretion of the treating clinical team.

Your baby will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same and to reduce bias it is important that each participant is put into a group by chance (random).

This research project has been designed in this way to make sure the researchers interpret the results in a fair and appropriate way and avoid study doctors or participants jumping to conclusions.

There are no additional costs associated with participation in this research project, nor will you or the participant be paid. All medical care required as part of the research project will be provided to your baby free of charge.

4 What does my baby have to do?

Your baby will be randomised to either the treatment or intervention group. According to randomisation, your baby will receive routine care or will taste and smell the milk before each tube feed. Data will be recorded about your baby's progress but there are no additional commitments required for your baby.

5 Other relevant information about the research project

A total of 330 preterm babies will take part in this research project, 165 in each group. Babies will be recruited at the Neonatal Critical Care Unit at the Mater Mothers' Hospital and at the Neonatal Intensive and Special Care at the Royal Women's Hospital, Melbourne. This project is a follow up from the previous pilot study called 'Smell and taste to improve nutrition in preterm infants: a randomised controlled pilot trial' and involves researchers from the Mater Mothers' and Royal Women's Hospitals and from the Mater Research Institute.

6 Does my baby have to take part in this research project?

Participation in any research project is voluntary. If you do not wish your baby to take part, they do not have to. If you decide that they may take part and later change your mind, you are free to withdraw your baby from the project at any stage.

If you do decide that your baby can take part, you will need to sign this Parent Information and Consent Form and you will be given a copy to keep.

Your decision that your baby may or may not take part or that they may take part and then be withdrawn will not affect their routine treatment, relationship with those treating them or their relationship with The Mater Mothers' Hospital.

7 What are the alternatives to participation?

Your baby does not have to take part in this research project to receive full treatment at this hospital.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that the child will receive any benefits from this research. However, possible benefits may include better tolerance of milk feeds and/or improved growth.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects, however, we are not aware of any issues associated with smell and taste of milk. In case your baby experiences any discomfort or side effects, or you are worried about them, talk with any of the staff. We will take your concerns seriously and will manage any discomfort and concerns related to the study.

If you or your baby becomes upset or distressed as a result of participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who is not members of the research project team. This counselling will be provided free of charge.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want your baby to continue in the research project. If you decide to withdraw your baby, their study doctor will make arrangements for their regular health care to continue.

11 Can the child have other treatments during this research project?

Your baby can have all other treatment during the research project. No restrictions are necessary.

12 What if I withdraw the child from this research project?

If you decide to withdraw your baby from the project, please notify a member of the research team before you withdraw them. This notice will allow that person or the research supervisor to discuss further any health risks or special requirements linked to withdrawing.

If you do withdraw your baby from the study, personal information already collected will be retained but no further data will be collected. This is to ensure that the results of the research project can be measured properly and comply with law. If you do not want the study team to use already collected data, you must tell them before your baby joins the research project.

You also have the option to withdraw your baby from the study procedure only and allow the research team to continue with data collection past the time point of withdrawal from the study procedure.

Mater Research

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects.

14 What happens when the research project ends?

Babies born at less than 28 weeks gestation or below 1000g are routinely offered developmental follow up at 1 and 2 years of age. We would like to collect data from those follow up assessments.
If you give us permission, we will contact you at ~ 1 year corrected age to ask how your baby is doing and about how long you breast fed.

Part 2 How is the research project being conducted?

15 What will happen to information about the child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your baby for the research project. Any information obtained in connection with this research project that can identify your baby will remain confidential.

Data will be stored de-identified under a study number on a password locked work computer. A list linking the study number to your baby's personal details will be kept in a locked cupboard in the Research Office. Your baby's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your baby may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your baby's participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums (e.g., conferences, journal articles, teaching presentations). In any publication and/or presentation, information will be provided in such a way that your baby cannot be identified, except with your permission. Confidentiality will be maintained as results will only be published in a de-identified manner.

Information about your baby's participation in this research project may be recorded in their health records.

In accordance with relevant Australian and Queensland privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member whose name appears at the end of this document if you would like to access your baby's information.

Any information obtained for the purpose of this research project that can identify your baby will be treated as confidential and securely stored. It will be disclosed only with your permission or as required by law.

16 Complaints and Compensation

If your baby suffers as a result of this research project, appropriate medical treatment for your baby will be arranged. If your baby is eligible for Medicare, they can receive any medical treatment required free of charge as a public patient in any Australian public hospital.

17 Who is organising and funding the research?

This research project is being organised and funded by the Mater Research Institute.

No member of the research team will receive a personal financial benefit from your baby's involvement in this research project (other than their ordinary wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Mater Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 07 3163 1918 or any of the following people:

Mater Research Nurse	Phone: 07 3163 8543
Human Research Ethics Committee	Phone: 07 3163 1585

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.
A copy of the information sheet and consent form is for you to keep.

Consent Form – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal Investigator	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital, South Brisbane

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my baby's doctors, other health professionals or hospitals outside this hospital to release information to the study team concerning my baby's disease and treatment for the purpose of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

☐ I freely agree to my baby's participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

☐ I agree to the collection of the results of my baby's 1 and 2 year follow-up developmental assessment (if performed)

☐ I agree to be contacted by a research nurse when my baby is 1 year old about the duration of breast feeding. I can change my decision any time.

I understand that I will be given a signed copy of this document to keep.

Name of Baby (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Name of Witness* to Parent/Guardian Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Form for Withdrawal of Participation – Parent/Guardian

Title	Smell and taste to improve nutrition in very preterm infants: a randomised controlled trial.
Short Title	TASTE trial
Protocol Number	HREC/16/MHS/112
Coordinating Principal	Dr Friederike Beker
Associate Investigators	A/Prof Helen Liley, A/Prof Luke Jardine, Dr Richard Mausling, Dr David Risson, Dr Kelly Dixon, Dr Paul Woodgate, Dr Maureen Dingwall, Dr Lucy Cooke, Prof Vicki Clifton, Dr Fiona Hutchinson, Ms Deborah Caldararo, A/Prof Sue Jacobs, Prof Peter Davis, Ms Emily Twitchell
Location	Neonatal Critical Care Unit, Mater Mothers' Hospital

Declaration by Parent/Guardian

I wish to withdraw the child from participation in the above research project and understand that such withdrawal will not affect their routine treatment, relationships with those treating them or the relationship with *the Mater Mothers' Hospital.*

I agree to data collection to continue past withdrawal from the study procedure: ☐ yes; ☐ no

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Description of circumstances:

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name	1

		of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1, sup 1
Protocol version	#3	Date and version identifier	1+9
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and	7

		statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	N/A

emergency unblinding		permissible, and procedure for revealing a participant's allocated intervention during the trial	
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1+9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	N/A

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public,	1+9

		and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7, sup 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A