EXPRESS: Expressing in PREmaturity – Simple interventionS
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EXPRESS
EXpressing in PREmaturity - Simple interventionS

Statistical Analysis Plan
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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
CONSORT	Consolidated standards of reporting trails
CRF	Case report form
CTU	Clinical trials unit
DMC	Data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
EDD	Estimated date of delivery
g	Gram
HMF	Human milk feeding/fed
IQR	Interquartile range
Max	Maximum
MD	Mean Difference
Med D	Median Difference
mg	Milligram
min	Minute
ml	Millilitre
MOM	Mother's Own Milk
NEC	Necrotising enterocolitis
NIHR	National Institute for Health Research
NNU	Neonatal unit
NPEU	National Perinatal Epidemiology Unit
PCL-5	Post-traumatic stress Checklist for DSM-5
PMA	Postmenstrual Age
ROC	Receiver Operating Characteristics
ROP	Retinopathy of Prematurity
RR	Risk Ratio
SAE	Serious adverse event
SD	Standard Deviation
STAI-6	Spielberger State-Trait Anxiety Inventory (shortened six item version)
VLBW	Very Low Birth Weight

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the NIHR-funded Randomised Controlled Trial of a guided relaxation audio recording targeted at lactation in mothers of very preterm babies (EXPRESS: Expressing in PREmaturity – Simple interventionS).

The results reported in the main paper(s) will follow the strategy set out here, and conforms to the published guidelines on the content for statistical analysis plans in clinical trials.[1] Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis nor to prohibit accepted practices, but they are intended to establish the rules that will be followed as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees will be considered carefully, and carried out as far as possible in line with the principles of this analysis plan; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out or supervised by an identified, appropriately qualified and experienced statistician. The person carrying out the analysis should ensure the integrity of the data during their processing.

2 BACKGROUND INFORMATION

2.1 Rationale

There are an estimated 2.4 million infants born at less than 32 weeks of post-menstrual age (PMA) globally[1] and the rate of premature birth is increasing[2]. Complications arising from premature birth are the leading cause of neonatal death in the UK[3] and globally[2], and prematurity increases the risk of long-term disability[4]. Parents of premature infants have higher rates of anxiety, depression and post-traumatic stress reactions than parents of healthy babies[5,6].

Infants born at less than 32 weeks of gestation cannot fully orally feed from birth and are therefore given nutrition intravenously and/or directly into the stomach with an enteral tube. To provide breastmilk for their infants, mothers must express milk from the breasts for a prolonged period. Maximising the volume of maternal breastmilk given to these infants improves mortality, morbidity and long term neurodevelopmental outcome[7–10]. Despite high motivation to provide expressed breastmilk for their infants, there is a high risk of poor milk supply, leading to non-exclusive human milk feeding[11–15] and an increasing failure to meet mothers' own goals for human milk provision as time goes on[16].

[1] Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017; 318:2337-43.

Although breastmilk feeding in prematurity has been identified as a top ten research priority by the James Lind Alliance priority setting partnership[17], there are few randomised controlled trials (RCTs) related to breastmilk expression[18]. Cochrane review noted that one promising technique to improve expressed milk yield is guided relaxation and visualisation by the mother and recommended further research in this area[18]. This RCT was therefore set up to test whether an audio recording with guided relaxation and visualisation content can help to increase expressed milk yield, maternal mental health and human milk feeding (HMF) outcomes.

2.2 Objectives and outcomes

Table 1: Trial Objectives and Outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary objective To compare the expressed milk yield in recording intervention and comparator groups	24-hour weight of expressed milk on maternal log (highest from specified timepoints)	Day 4, day 14 and day 21 of baby's life
Secondary Objectives To compare the achievement of target expressed milk yield in recording intervention and comparator groups	Proportion expressing at least 750g milk in 24 hours, on maternal log on any of the specified timepoints	Day 4, day 14 and day 21 of baby's life
To compare expressing efficiency in recording intervention and comparator groups	Average volume of milk expressed per minute over 24 hours, on maternal log	Day 21
To compare maternal anxiety in recording intervention and comparator groups	Average maternal anxiety score (Spielberger State Trait Anxiety Index six-item self-report questionnaire)	Day 21
To compare maternal trauma related distress in recording intervention and comparator groups	Average maternal distress score (Post-traumatic stress Check List for DSM-5)	Day 21
To compare exclusive human milk feeding in recording	Proportion with exclusive human milk feeding by maternal report/from medical notes (no	36 weeks' PMA

intervention and comparator groups	intake of infant formula in last 24 hours)	
To compare any human milk feeding in recording intervention and comparator groups	Proportion with exclusive human milk feeding by maternal report (no intake of infant formula in last 24 hours)	18 weeks after EDD (4 months' corrected age)
	Proportion with any human milk feeding in last 24 hours by maternal report/from medical notes	36 weeks' PMA
Process indicators	Time spent in skin to skin contact with any of the participant's infants in 24 hours by maternal report (hours)	Day 21
	Number of expressing episodes in 24 hours by maternal report	Day 21
	Time spent expressing in 24 hours by maternal report (hours)	Day 21

2.3 Trial design

This is a non-blinded randomised controlled trial with parallel design taking place in three NHS trusts. The entire recruitment and follow up period of the trial will take 18 months to complete and the trial aims to recruit 132 mothers of very preterm infants.

For reasons of efficiency within the available time, the recruitment period is divided into two sections. The majority of recruitment will take place in the 'complete follow up' period where participants will complete all outcome data points up to 18 weeks after the estimated date of delivery (EDD). The final 22 weeks of recruitment will form the 'abbreviated follow up' period where participants will end the study when their infant is 36 weeks' PMA. This will result in a smaller group of participants who are assessed for the final trial outcome of exclusive HMF at 18 weeks after the EDD.

2.4 Eligibility

Inclusion Criteria:

- Mother has one or two live infants born at 23^{+0} to 31^{+6} weeks of gestation
- Infant/s inpatient on a recruiting neonatal unit
- Willing and able to give informed consent for participation in the study
- Aged 18 years or above
- Infant/s will be less than 4 days of age at time of enrolment
- Mother intends to express milk for at least 14 days
- Mother has a device on which she can listen to an MP3 file

Exclusion Criteria:

- No dating scan antenatally
- Triplet or higher order pregnancy with more than two live born infants

2.5 Intervention

The intervention is the provision of a specific audio recording to the participant with a request to listen to the track during expression of milk as often as possible while expressing milk, for at least three weeks. Participants will be sent a reminder text message on day 9 and day 17 to promote continued listening. The intervention audio track will last for approximately 12 minutes and consist of a guided relaxation and expression-specific visualisation – this is an adapted version of an existing soundtrack used for previous studies[19–22], modified and used under license from the original author. The visualisation includes descriptions of pleasant surroundings, milk flowing in the breasts, and skin to skin contact with the infant. The audio track will be provided as a downloadable mp3 file, with the option of an mp3 file on a USB stick if required. Participants will be asked not to share the file with anyone else during the study. They can continue listening to the track throughout the study period and beyond if they so desire.

In addition, the recording intervention group will receive the same standard care as the comparator group, including lactation advice from neonatal unit staff and infant feeding team and standardised printed information describing best-practice information on how to express milk for a preterm infant[23]. It is standard care to encourage skin-to-skin contact between mother and infant/s for many reasons, including because of its positive impact on milk supply and establishment of breastfeeding.

2.6 Hypothesis framework

Participants will be analysed in the groups to which they were randomly assigned, comparing the outcome of all infants allocated to the recording intervention with all those allocated to the comparator group, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat or ITT population). All analyses are performed on a superiority basis.

2.7 Sample size & power

Previous work has shown increase in yield with audio relaxation intervention of between 60% and 270%[19,33]. Meta-analysis by the Chief Investigator of eight studies gave a standardised mean difference of 0.7 - this means an increase in milk yield of 0.7 standard deviations with use of relaxation. In the most relevant study[19], mean yield at day 14 increased from 318ml ± 309ml to 862ml ± 309ml with the use of a visualisation/relaxation soundtrack (mean difference in 24 hour yield of 544ml).

Exploratory work in the Thames Valley suggested that baseline milk yield is higher and more variable than seen in that trial (audit of retrospectively reported expressed milk volumes on day 14 showed mean of 628ml ± 465ml), although the standard deviation is likely to be overestimated due to small sample size (n=32). The study is therefore powered to detect an increase in maximum expressed milk yield from 670g ± 300g to 825g ± 300g (23% increase; mean difference of 155g; standardised mean difference of 0.5), with 80% power and a two-sided significance level of 0.05. 118 participants are required at day 21 [total recruitment target is 132 to allow 10% loss to follow up].

Note that human milk has an average specific gravity of 1.03[34] therefore 670g is estimated as equivalent to 650ml and 825g is estimated as equivalent to 800ml – although many studies regard the mass and volume of human milk as equivalent[35].

2.8 Intervention allocation

Participants will be randomised using stratified permuted block randomisation. Stratification will be based on centre, gestational age at birth (23^{+0} to 27^{+6} weeks versus 28^{+0} to 31^{+6} weeks) and multiple birth (one baby alive at time of randomisation versus two babies alive at time of randomisation).

2.9 Data collection schedule

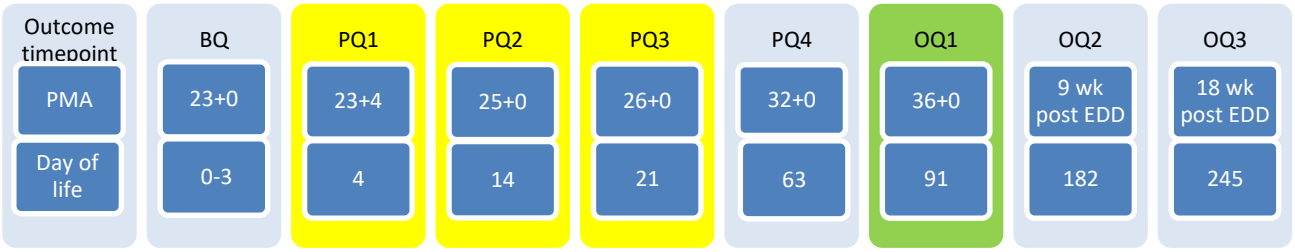
Table 2: Trial Procedures

Procedures							
	From day of birth (day 0) up to midnight on day 3 of life	Day 4, 14	Day 4-7	Day 21	32 week PMA	36 week PMA	9 & 18 weeks after due date
					If born <27 wks only		*'Complete follow up' recruitment period only*
Informed consent	✓						
Eligibility assessment	✓						
Randomisation	✓						
Baseline Questionnaire (BQ)	✓						
Trial Entry Form (TEF)	✓						
Maternal training and assessment on use of scales	✓						
Check-in and verify accurate use of scales (D4-7 check in)			✓				
Questionnaire & 24-hour expressing log (PQ1-4)		✓		✓	✓		

Maternal mental health questionnaires				✓			
Text message response (OQ1-3)						✓	✓

Figure 1: Timeline for most and least preterm infant eligible. Potential primary outcome timepoints shown in yellow, end of study for those recruited in the 'abbreviated follow up' period shown in green

Most preterm infant eligible:

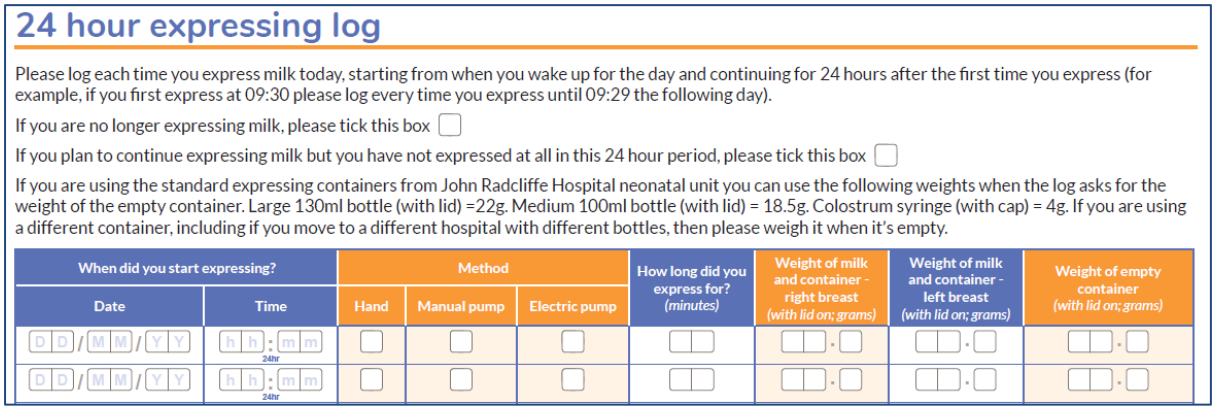


Least preterm infant eligible:

Data is predominantly collected via electronic case report forms (eCRFs). Paper CRFs are available for some timepoints if desired by participants (BQ – baseline questionnaire and PQ1-4 - expressing log/questionnaires).

Figure 2 and Figure 3**Error! Reference source not found.** show the expressing log that participants are requested to fill out at each timepoint, either on paper or electronically. This shows that each time the participant expresses milk they are asked to record the date and time that they started, the expressing method, the number of minutes they spent expressing and the weight of milk (and its container) produced by each breast. If they express a single breast then they provide a single weight of milk (and its container). If they express both breasts simultaneously (the recommended method) then they provide two weights of milk, each including the container (the container is assumed to be the same weight for both breasts).

The final piece of information recorded is the weight of the empty container so that pure milk weights can be calculated at the analysis stage. If the participant is using standard containers provided by the recruiting neonatal unit then the weights are provided in text format on the log, as shown in Figure 3.



24 hour expressing log

Please log each time you express milk today, starting from when you wake up for the day and continuing for 24 hours after the first time you express (for example, if you first express at 09:30 please log every time you express until 09:29 the following day).

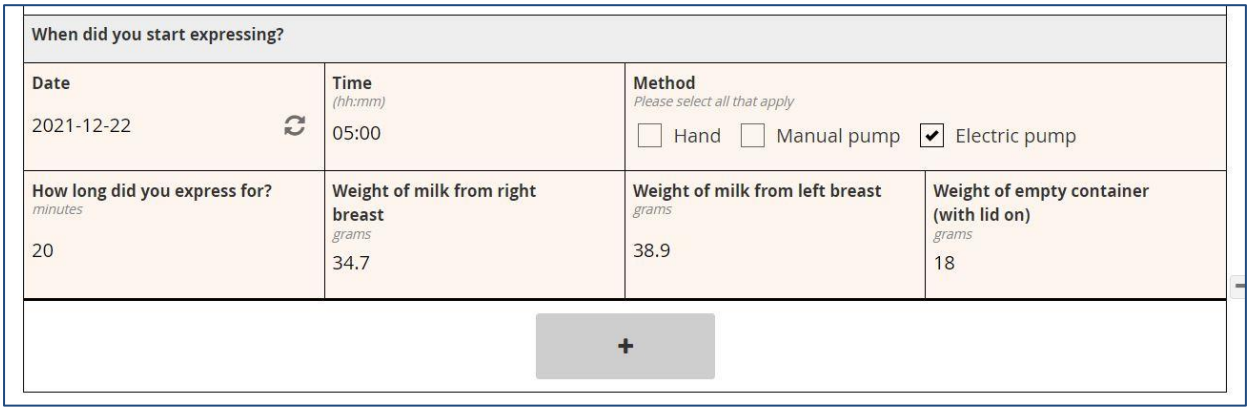
If you are no longer expressing milk, please tick this box ☐

If you plan to continue expressing milk but you have not expressed at all in this 24 hour period, please tick this box ☐

If you are using the standard expressing containers from John Radcliffe Hospital neonatal unit you can use the following weights when the log asks for the weight of the empty container. Large 130ml bottle (with lid) =22g. Medium 100ml bottle (with lid) = 18.5g. Colostrum syringe (with cap) = 4g. If you are using a different container, including if you move to a different hospital with different bottles, then please weigh it when it's empty.

When did you start expressing?		Method			How long did you express for? *(minutes)*	Weight of milk and container - right breast *(with lid on; grams)*	Weight of milk and container - left breast *(with lid on; grams)*	Weight of empty container *(with lid on; grams)*
Date	Time	Hand	Manual pump	Electric pump				
D D / M M / Y Y	h h : m m (24hr)	☐	☐	☐		.	.	.
D D / M M / Y Y	h h : m m (24hr)	☐	☐	☐		.	.	.

Figure 2: Extract from blank paper expressing log filled out by participants



When did you start expressing?

Date	Time	Method	
2021-12-22	05:00 *(hh:mm)*	*Please select all that apply* ☐ Hand ☐ Manual pump ☑ Electric pump	
How long did you express for? *minutes* 20	**Weight of milk from right breast** *grams* 34.7	**Weight of milk from left breast** *grams* 38.9	**Weight of empty container (with lid on)** *grams* 18

\+

Figure 3: Mock-up of electronic expressing log provided to participants

2.10 Data monitoring, interim analyses and stopping rules

The Data Monitoring Committee (DMC) will consider accumulating information relating to safety, recruitment and data quality (e.g. data return rates, treatment adherence, protocol adherence, withdrawal). Unblinded group data will be available to the DMC to assess baseline comparability, differential withdrawal/data quality and assumptions used in powering the study but no statistical tests will be performed due to the size of the trial and there are no pre-specified stopping rules. An interim meeting will occur after six to nine months of trial recruitment. A report will be prepared by an independent trial statistician.

2.11 Trial reporting

The trial will be reported according to the principles of the CONSORT statement. Data lock will occur in two stages – first data lock will occur once data entry is complete and all queries have been resolved related to the period up to and including day 21 forms for the last participant recruited (PQ3). Final data lock will occur once data entry is complete and all queries have been resolved related to the final chronological timepoint for all participants (OQ1 for those recruited in the 'abbreviated follow up' period and OQ3 for those recruited in the 'complete follow up' period)

3 PROTOCOL NON-COMPLIANCES

A protocol non-compliance is defined as a failure to adhere to the protocol such as the wrong allocation being administered, incorrect data being collected and documented, errors in applying inclusion/exclusion criteria or missed follow-up visits due to error.

All protocol non-compliances will be listed in the final report. Non-compliances are defined below.

3.1 Major

The following are pre-defined major protocol non-compliances with a direct bearing on the primary outcome:

- Data considered to be fraudulent

3.2 Minor

The following will be defined as minor protocol non-compliances:

- Participants randomised in error. These include participants:
  - With infants born < 23 weeks' or ≥ 32 weeks' PMA
  - With infants ≥ 4 days old
  - With more than two live infants
  - Aged under 18 years
  - With no antenatal dating scan
  - Where written informed consent has not been obtained
- Treatment non-compliances. These include participants who:
  - Are in the recording intervention group and do not receive the study recording
  - Are in the recording intervention group and receive the study recording more than 4 days after birth
  - Are in the control group and receive the study recording
- Trial procedure non-compliances:
  - Trial Entry Form not completed by site staff
  - Day 4-7 check in not completed by site staff within scheduled window
  - Participant entered data not completed within scheduled windows
  - Are in the recording intervention group and never listen to the study recording
  - Are in the control group and regularly listen to or practice independently sourced guided relaxation material

Protocol non-compliances will be reported in a flowchart and process outcomes table.

4 ANALYSIS POPULATIONS

4.1 Post-randomisation exclusions

Exclusions to the analysis post-randomisation are defined as any of the following:

- Participants for whom a written consent form was not received
- Participants whose consent to use their data was withdrawn (excluded from the point of withdrawal)
- Participants for whom an entire record of fraudulent data was detected (should fraudulent data be detected, consideration will be given to excluding all data for the site where such data were found).

The numbers and proportion of post-randomisation exclusions will be reported by randomised treatment group, and reasons summarised.

4.2 Population definitions

The intention to treat (ITT) population will be all participants randomised, excluding post-randomisation exclusions. Note that the population assessed for the final trial outcome (exclusive HMF at 18 weeks after the EDD) is formed of only the participants recruited in the complete follow up period, not the abbreviated follow up period.

In the interim analysis, baseline and outcome data will be reported for all trial participants with available data, excluding known post-randomisation exclusions.

5 DESCRIPTIVE ANALYSES

5.1 Representativeness of trial population and participant throughput

A flow diagram will be reported showing number of participants randomised, allocated and providing data at each timepoint, as well as number providing data for the primary outcome analysis. Post-randomisation exclusions and specifically a change of consent (withdrawal) due to infant/s death and other reasons will be presented. Number of participants in the complete follow up period and the abbreviated follow up period will be reported. Measurements of recording intervention adherence and contamination will be reported in table format (number of participants in recording intervention group reporting never listening to recording on day 4 or day 14 or day 21 questionnaires; number of participants reporting listening to/practising other relaxation material in trial period at day 21). Reporting will follow CONSORT guidance.

5.2 Baseline comparability of randomised groups

The intention to treat analysis population will be used and all baseline characteristics reported in table format.

The following maternal characteristics will be described in the baseline tables:

- Ethnicity
- Age at randomisation
- Deprivation index quintile
- Age at leaving full time education
- Living with a partner
- Current smoker
- Admitted to ITU in first 48 hours after birth
- Time from birth to first expression of milk
- Intention for exclusive HMF at the time of discharge
- STAI-6 score
- Mode of delivery
- Parity
- Previous HMF experience (binary and length of longest previous HMF)

The following infant characteristics will be described in the baseline tables:

- Recruiting centre at randomisation

- Place of birth (randomisation centre or not)
- Gestational age at birth
- Age at randomisation
- Single or twin birth
- Apgar score at five minutes
- Ventilated at randomisation

If a participant has two babies, the most invasive birth method, the most invasive respiratory support and the lowest Apgar score of the two babies is reported.

Categorical data will be presented using counts and percentages, continuous data will be presented using number of participants, mean, median, standard deviation, minimum, maximum and/or interquartile range. There will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline variable.

STAI-6 score at baseline will in addition be presented as number and percentage of participants with score >40. Time after birth at randomisation will be presented by group. Participant postcode is transformed to quintiles of index of multiple deprivation using publicly available calculators.

5.3 Losses to follow-up

Change of consent (withdrawal) and loss to follow up will be reported in the flowchart as mentioned above. A moderate level of loss to follow up is expected as the study relies on participant reported outcomes at a time of high stress. Infant mortality of 10% is expected, with associated withdrawal – although part of the impact is expected to fall after data has been contributed for the primary outcome.

Any baseline information collected on losses to follow-up may be compared with those who completed the trial to the primary outcome and presented using summary statistics.

5.4 Adherence to recording intervention

Adherence with the recording intervention will be reported in the process indicator tables (number of times listened to the study recording in previous 24 hours at each log timepoint). An assessment of whether participants in both arms have practiced non-intervention relaxation in the study period as assessed at day 21 is also reported.

6 COMPARATIVE ANALYSES

6.1 Detailed definition of primary outcome

Primary outcome: 24-hour weight of expressed milk

On day 4, day 14 and day 21 after birth, participants are requested to record all the milk that they express in a 24-hour period, by weight. The weight of expressed milk reported at all sessions within each 24-hour period is summed to produce a 24-hour weight for each timepoint. The primary outcome is the highest calculated 24-hour milk weight from any of the three timepoints. Examples are shown in `Table 3`.

Table 3: Defining the highest 24-hour weight for primary outcome assessment

	Day 4	**Day 14**	**Day 21**	**Primary Outcome**
Scenario 1	300g	500g	750g	750g
Scenario 2	100g	450g	400g	450g
Scenario 3	50g	missing	missing	50g
Scenario 4	50g	150g	Stopped expressing (0g)	150g

The following is a step by step description of how data is extracted from the participant log (pictured in `Figure 2` and `Figure 3`**Error! Reference source not found.**) to derive the 24-hour weight:

- The pure milk weight expressed at each session is calculated by subtracting the weight of the empty container from each combined milk/container weight recorded.
- If this pure milk weight is negative (the container is recorded as heavier than the combined milk/container weight) then the value is classified as erroneous data. However if a single combined milk/container weight is recorded as zero then the pure milk weight will be classified as missing data instead
- If there is no container weight recorded then the value is classified as erroneous data
- The 24-hour period is defined as the 24 hours following the start time of the first chronologically recorded log. Expressing sessions are included in the 24-hour yield if they are completed (defined by the end time of the expressing session) in ≤24 hours from the start time
- The 24-hour yield at each timepoint is calculated by summing all non-erroneous milk weights in the 24-hour period

Examples of defining the 24-hour period are shown in `Table 4`:

Table 4: Defining the 24-hour period for primary outcome assessment

Potential scenario	**Analysis impact**
Participant starts expressing at 10am 12/02/2022. Final log recorded finishes at 10am 13/02/2022	Milk expressed at final log is included in 24-hour total
Participant starts expressing at 10am 12/02/2022. Final log recorded finishes at 10:01am 13/02/2022	Milk expressed at final log is not included in 24-hour total

Examples of defining erroneous data are shown in `Table 5`:

Table 5: Erroneous data definition

Potential scenario	**Analysis impact**
Participant records a single expressing session [milk + container] weight as 10g and the container weight as 13g	The milk weight for this session is -3g and is classified as erroneous

Participant does not submit the container weight for an expressing session	The milk weight for this session is classified as erroneous
Participant records a valid weight for the right breast [milk + container] and records 0 for the left breast (perhaps as they have not attempted to express the left breast or have combined milk from both breasts into one bottle)	Zero is treated as missing data, not erroneous data. The milk weight for this session contributes to the 24 hour yield.
Participant records 0 [milk + container] weights for both breasts	The milk weight for this session is classified as erroneous

If a participant has reported that no attempt to express milk has been made in the 24-hour period (tickbox options shown in Figure 2), this will contribute a value of 0g as the 24-hour weight. If a participant has not provided a log, the value is missing.

After the 24-hour milk yield has been calculated for each timepoint, the primary outcome is identified as the highest of these values as noted above and shown in Table 3. Further detail is given in Table 6 for a variety of scenarios.

Table 6: Potential expressing log scenarios and their analysis impact

Potential scenario	**Analysis impact**
Three logs have been submitted (optimal scenario)	Primary outcome is the highest 24-hour total of the submitted logs
Participant does not submit a log at one or two timepoints	24-hour total is recorded as missing for any timepoints where a log is not submitted. The primary outcome is the highest of the submitted logs
Participant does not submit a log at any timepoint	Primary outcome is missing
Participant reports that they have not attempted to express milk in the 24-hour period for a log	24-hour total is 0g for this log
Two logs have been submitted and one reported as no attempt to express milk in the 24-hour period	Primary outcome is the highest 24-hour total of the submitted logs, including the log with 0g 24-hour total
One or two logs are recorded as no attempt to express milk in the 24-hour period and the other log is missing	Primary outcome is 0g
All logs are recorded as no attempt to express milk in the 24-hour period	Primary outcome is 0g

Details of which timepoint forms the primary outcome will be presented by group with no statistical test, as well as details of which timepoints were available (non-missing) for the assessment of the primary outcome.

Logs will be included in the analysis for the scheduled timepoint regardless of the date of data that they refer to. For example if a participant submits a day 4 log and the data refers

to day 7, it will be included in the analysis as a day 4 log. The number of logs falling outside the scheduled 48-hour window for each timepoint will be presented.

10am is used as an arbitrary scheduled start time for each logging timepoint to define the 48-hour window (for example a day 4 log will fall outside the scheduled window if the first logged expressing session starts before 10am on day 6).

Some participants unexpectedly expressed both breasts sequentially into the same container. This poses a problem to the format of the expressing log as milk weight is requested inside a separate container for each breast. Where this was noted by the researchers or raised by the participant, the participant was advised to allocate this milk/container weight to a single breast. No further analysis of milk weight by breast is used because of this potential inaccuracy in milk assigned to a specific breast. This does not affect the primary outcome.

Some participants unexpectedly expressed such a high quantity of milk that they required more than one bottle for each breast at a single expressing session. This poses a problem to the format of the expressing log as milk weight is requested as a single container of milk for each breast for each session. Where this was noted by the researchers or raised by the participant, the participant was advised to record multiple sessions with precise, non-overlapping start time and duration to match the time spent expressing milk into each set of containers. However in some cases participants logged multiple sessions with identical start time and duration, or with overlapping times and duration, or with zero duration, to deal with this scenario. This does not affect the primary outcome.

6.2 Detailed definition of secondary outcomes

Secondary outcome: Proportion expressing at least 750g milk in 24 hours
The highest 24-hour milk weight forming the primary outcome is used to define whether the participant has expressed ≥750g in any of the recorded 24-hour periods.

Secondary outcome: Average volume of milk expressed per minute
The 24-hour milk weight recorded at day 21 is divided by the number of minutes spent expressing in 24 hours at day 21 to form this outcome.

As noted above, there are some scenarios which affect the calculation of an accurate milk expression rate – these are when erroneous data have been identified and where participants have used more than one container for each breast during a single expressing session and may have logged this in a variety of ways. To ensure that the appropriate numerator and denominator are used in these cases, the following exclusions apply for this outcome:

- Where an expressing session includes erroneous data (as defined in section 6.1 and in Table 5) then the whole session is excluded from the numerator (any milk weight associated with the session) and the denominator (any time associated with this session)
- If both start time and duration for multiple logged sessions are identical then the duration of duplicate sessions will be excluded from the denominator

Secondary outcome: Proportion with exclusive human milk feeding
This outcome is assessed at two separate timepoints – 36 weeks' PMA and 18 weeks after the EDD. Exclusivity of human milk feeding will be defined as no intake of infant formula in the reference period (the 24 hours prior to the question being asked). If a participant has two babies, the outcome will be classified with reference to both infants (no infant formula given to either infant). Of note, intake of complementary food is not considered in this outcome. Participants respond to an SMS message to provide this information. At 36 weeks', this information can also be derived from the infant's medical notes where an SMS response is not received.

SMS responses will be included in the analysis for the scheduled timepoint regardless of the date that they are sent. For example, if a participant responds to the 36 week PMA SMS at 38 weeks PMA, it will be included in the analysis as a 36 weeks PMA response. The number of responses falling outside the scheduled 7-day window for each timepoint will be reported. The number of responses derived from infant medical notes will be reported.

If the participant has reported at an earlier time point that they are no longer lactating (on an expressing log) or no longer human milk feeding (by SMS), then later SMS timepoints will also be defined as no exclusive human milk feeding.

Secondary outcome: Proportion with any human milk feeding
This outcome is assessed at 36 weeks' PMA with the same process as above. It is defined as any human milk intake in the reference period (the 24 hours prior to the question being asked). If a participant has two babies, the outcome will be classified with reference to both infants (any human milk intake by either infant).

If the participant has reported at an earlier time point that they are no longer lactating (on an expressing log) or no longer human milk feeding (by SMS), then later SMS timepoints will also be defined as no human milk feeding.

Secondary outcome: Average maternal anxiety score
Maternal anxiety will be measured by the STAI-6, at baseline and day 21. The outcome is formed by the day 21 average score, adjusted for baseline. The original Spielberger State Trait Anxiety Index (STAI) is a 20-item questionnaire with four answer options for each question ('not at all', 'somewhat', 'moderately' or 'very much') and a score of 1–4 for each question (order of score allocation depends on whether question item is positive or negative). The total score range is 20–80, with higher scores signifying more anxiety, <36 generally considered normal[24] and >40 signifying clinically significant anxiety[25]. The shortened STAI-6 contains a subset of six questions, giving a score total of 6–24, which are then scaled to 20–80 for comparability[26]. The short form is highly correlated with the 20-item STAI, with internal consistency greater than 0.9[27]. The minimal meaningful difference in STAI score has been suggested as 10[28].

Secondary outcome: Average maternal distress score
Maternal stress reaction to the trauma of preterm birth will be measured by the PCL-5 at day 21. The Post-traumatic stress Check List for DSM-5 (PCL-5)[29] has 20 items with four answer options for each question ("not at all", "a little bit", "moderately", "quite a bit" and

"extremely") and a score of 0–4 for each question. The total score range is 0–80, with higher scores signifying more distress. A cut off of 31–33[3031] has been proposed as indicative for probable PTSD. A minimal meaningful impact of treatment has been suggested as bringing the total score down below 24[30], although this should be used with caution. An alternative approach is that a 5–10 point change is likely to be the minimum threshold for a clinically meaningful difference[29]. The PCL-5 has internal consistency (for example Cronbach's alpha 0.95) and good construct validity in a variety of settings[30–32] although of necessity the evidence is limited because of its more recent modification to align with DSM-5 criteria.

Process indicator: Time spent in skin-to-skin contact with infant

This indicator is measured by questionnaire on day 21. It is measured in number of hours of skin to skin contact by the participant with any of her infants (that is, the sum of the hours spent in skin to skin contact by the participant with both infants if there are two).

Process indicator: Number of expressing episodes

This indicator is measured via the expressing log on day 21. It is the number of episodes of expressing recorded by the participant in a 24-hour period. The 24-hour period is defined as per the primary outcome. Expressing two breasts simultaneously is recorded on the log as one expressing episode.

As noted above, the way in which participants record sessions where they have used more than one container for each breast will affect the calculation of an accurate number of expressing episodes. Therefore, the following exclusions apply for this outcome:

- Where an expressing session has been recorded with duration of zero minutes, it will be excluded
- Where the start time and duration of expressing sessions are identical, duplicate sessions will be excluded
- Where the start time of an expressing session is within the duration of a prior session (i.e. the session timings overlap), the later session will be excluded
- Where the start time of an expressing session is less than 10 minutes after a prior session is completed, the later session will be excluded

Process indicator: Time spent expressing

This indicator is measured via the expressing log on day 21. It is the sum of the number of minutes recorded for each expressing session in a 24-hour period. The 24-hour period is defined as per the primary outcome. The following exclusion applies to this outcome:

- Where the start time and duration of expressing sessions are identical, duplicate time will be excluded

Process indicators without statistical inference

In addition to the process indicators listed individually above and in Table 1, several other process indicators will be reported with summary statistics and without statistical inferences. These are:

- Perception of low milk supply on day 21 (defined by response to the question "How do you feel about your milk supply today?" of "I think I don't have enough milk")
- Number of direct breastfeeds on day 21 (defined by response to the question "Thinking of the 24-hour period starting at 0800 yesterday, how many direct breastfeeds did your baby have, if any? Define a breastfeed as an episode at the breast where you felt the baby was sucking and swallowing some milk. If the baby is offered both breasts at a single episode this is one breastfeed. If the baby stops sucking or swallowing for 30 minutes or more, then any further feeding is a new breastfeed. Please add up all the episodes if you have two babies.")
- Time spent in skin to skin contact in 24 hours on day 14 (defined as above)
- Expressing episodes in 24 hours on day 14 (defined as above)
- Time spent expressing in 24 hours on day 14 (defined as above)
- Perception of low milk supply on day 14 (defined as above)
- Number of direct breastfeeds on day 14 (defined as above)

6.3 Primary analysis

Intention to treat population will be used. Statistical analysis will use linear regression with adjusted and unadjusted mean differences presented, or quantile regression with median differences presented, as appropriate, along with associated 95% confidence intervals. Analyses will be adjusted for stratification factors used at randomisation.

The primary outcome and any secondary outcomes using the highest 24-hour milk weight will be adjusted for the day associated with the highest 24-hour milk weight.

6.4 Secondary analyses

Intention to treat population will be used throughout. Statistical analysis of continuous outcomes will use linear regression with adjusted and unadjusted mean differences presented, or quantile regression with median differences presented, as appropriate. Binary outcomes will be analysed using log binomial regression, or Poisson regression with a robust variance estimator if the model fails to converge, and risk ratios will be presented. 95% confidence intervals will be presented. Analyses will be adjusted for stratification factors used at randomisation.

Statistical inferences will be made for all the outcomes and process indicators listed in Table 1.

STAI-6 score at day 21 will be adjusted for baseline STAI-6 score. Analysis of STAI-6 and PCL-5 scores will use total score. Number/proportion of participants with STAI-6 score >40 and PCL-5 score >33 will also be reported with no statistical testing.

No statistical inferences will be made for the additional process indicators listed in section 6.2.

6.5 Pre-specified subgroup analyses

Pre-specified subgroup analyses will be performed for the primary outcome and two secondary outcomes: exclusive HMF at 36 weeks' PMA; and any HMF at 36 weeks' PMA as follows:-

- According to the stratified groupings for gestational age (23 to 27 weeks' PMA versus 28 to 31 weeks' PMA). Statistical testing using an interaction test will be used for the primary outcome only, reporting the adjusted effect estimate and 95% confidence intervals. This is important as it is generally reported that more mothers of extremely premature babies have worse expressing and HMF outcomes than mothers of very premature babies, and mothers of extremely premature babies may be more anxious and distressed due to the higher risk of morbidity and mortality as gestation decreases. The pre-specified hypothesis is that mother of more preterm babies will see a greater effect of the recording intervention due to their increased level of anxiety. However the reverse effect would not be unexpected as the physiological challenges faced by mothers of the more preterm babies (due to the very early stage of pregnancy related changes in breast tissue and lactation hormones) may be less amenable to relaxation as an intervention.

- According to the stratified grouping of number of babies alive at time of randomisation (one versus two), with no statistical testing. This is important as mothers of multiples are likely to target higher milk yield and need to establish a higher milk supply to be able to exclusively breastfeed two babies, but may have lower intention to human milk feed and have less time to listen to the recording intervention.

- According to intention to exclusively HMF at discharge, reported by participants at baseline (intention for exclusive HMF versus no intention or unsure), with no statistical testing. This is important as participants with no intention to exclusively breastfeed may make an informed choice to use infant formula even though they have established a good milk supply, and/or may make an informed choice to express more infrequently.

Within the recording intervention group only, the primary outcome will be presented for participants with high and low adherence with the intervention. High adherence is defined as listening to the recording two or more times a day on any non-missing timepoint (day 4, 14 or 21). Low adherence is defined as listening less than twice a day on all non-missing timepoints (day 4, 14 and 21). If this definition is impractical, median values will be used instead. This will be presented as summary statistics, with no statistical inference. Baseline characteristics associated with adherence will also be presented.

Within the recording intervention group only, the primary outcome will be presented for participants reporting that the recording made them feel relaxed at any non-missing timepoint (day 4, 14 or 21) compared with those who felt no change or less relaxation on all non-missing timepoints (day 4, 14 and 21). If this definition is impractical, median values will be used instead. This will be presented as summary statistics, with no statistical inference. Baseline characteristics associated with perception of the intervention will also be presented.

6.6 Sensitivity analyses

Statistical inferences will be used for the following sensitivity analyses:-

To assess for potential bias due to the distribution of the timepoints of logs used for the primary outcome by group, the primary outcome analysis will be repeated using only day 21 data. For example, there could be increased loss to follow up in one group and therefore increased use of earlier timepoint logs as the primary outcome which are likely to be lower weight and could therefore bias the primary outcome.

To assess for potential bias due to treatment dilution effect, the primary outcome analysis will be repeated without day 4 logs. This is because participants start the recording intervention between day 0 and day 3 after birth and it is therefore unlikely that a difference in milk yield would be seen as early as day 4.

To assess for potential bias due to incomplete logs, the primary outcome analysis will be repeated excluding any logs reporting less than four expressing sessions.

To assess for potential bias due to the timing of expressing logs, the primary outcome analysis will be repeated excluding any logs submitted outside the scheduled 48 hour window.

Sensitivity analysis relating to missing data is discussed below.

6.7 Comparison of eligible and recruited population

Demographic characteristics of the pooled trial population will be compared with aggregate data from the potentially eligible population without statistical inferences, using local routinely collected clinical data (Badgernet, Clevermed). The potentially eligible population is defined as:

- Born between 23+0 and 31+6 weeks of gestation
- Baby is born at one of the recruiting units or transferred into a recruiting unit on day 0, 1 or 2 of life
- Baby is a singleton birth or one of twins

The following demographic characteristics will be described for the firstborn infant (representing the mother – because data is entered into the clinical database using the infant as the unit of measurement whereas the trial recruits mothers as individuals):

- Gestational age at birth
- Parity (primiparous or multiparous)
- Multiple pregnancy
- Mode of delivery
- Mother's age

6.8 Significance levels and adjustment of p-values for multiplicity

95% confidence intervals will be used for all pre-specified outcome comparisons.

Acknowledging the issue of multiple testing and the small size of the study, we have limited the number of trial outcomes tested with statistical inferences to 11 in total. There will be no formal adjustment for multiplicity.

6.9 Missing data

Missing data includes variables that were not provided by participants and erroneous milk volumes that have been excluded (less than zero, or where no empty container weight has been recorded). The analysis will be performed on a complete case basis initially (i.e. only variables that have been provided will be analysed).

Given the reliance on participant-entered data for all outcomes and a significant likelihood of data being missing not at random, missing data may have a significant effect on conclusions. Sensitivity analysis will be performed to explore the pattern of missingness for the primary outcome, using multiple imputation and/or a pattern mixture model as appropriate. Statistical inferences will be made to assess the impact of missing data.

All missing data will be reported and described for each outcome and baseline characteristic. Baseline characteristics may be compared for those with missing expressing logs at day 4, 14 and/or 21 but with a primary outcome assessment, and those with complete expressing logs. These will be presented using summary statistics.

Data submitted before a change of consent/withdrawal will be used for analysis, unless the withdrawal is due suspicion of fraudulent data. This is in line with the stated reason for data processing during the consent process of 'a task in the public interest' (research).

6.10 Statistical software employed

Stata/SE will be used for statistical analysis.

7 SAFETY DATA ANALYSIS

Safety reporting is not required for this trial due to the nature of the recording intervention. Themes from any negative free text comments will be summarised.

8 ADDITIONAL EXPLORATORY ANALYSIS

Analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan. Post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such.

9 DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

None yet.

10 REFERENCES

10.1 Trial documents

EXPRESS trial protocol v5.0 26/05/2022
EXPRESS dummy tables v1.0 13/05/2022
SOP ST105: Statistical Analysis Plan
SOP ST107: Statistical Analysis and Reporting

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11 APPROVAL

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12 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to interim analysis/monitoring /unblinding
1.0	07/09/2022	original	Submitted for sign off before database lock. Note error in version numbers previously for draft SAPs shown to interim Trial Steering Committee, explained fully in Trial Master File filenote – this is the first SAP to be signed off and therefore is v1.0	All authors and signatories remain blinded. DMC members were unblinded for interim analysis without statistical inferences in February 2022 but had no input to the SAP

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