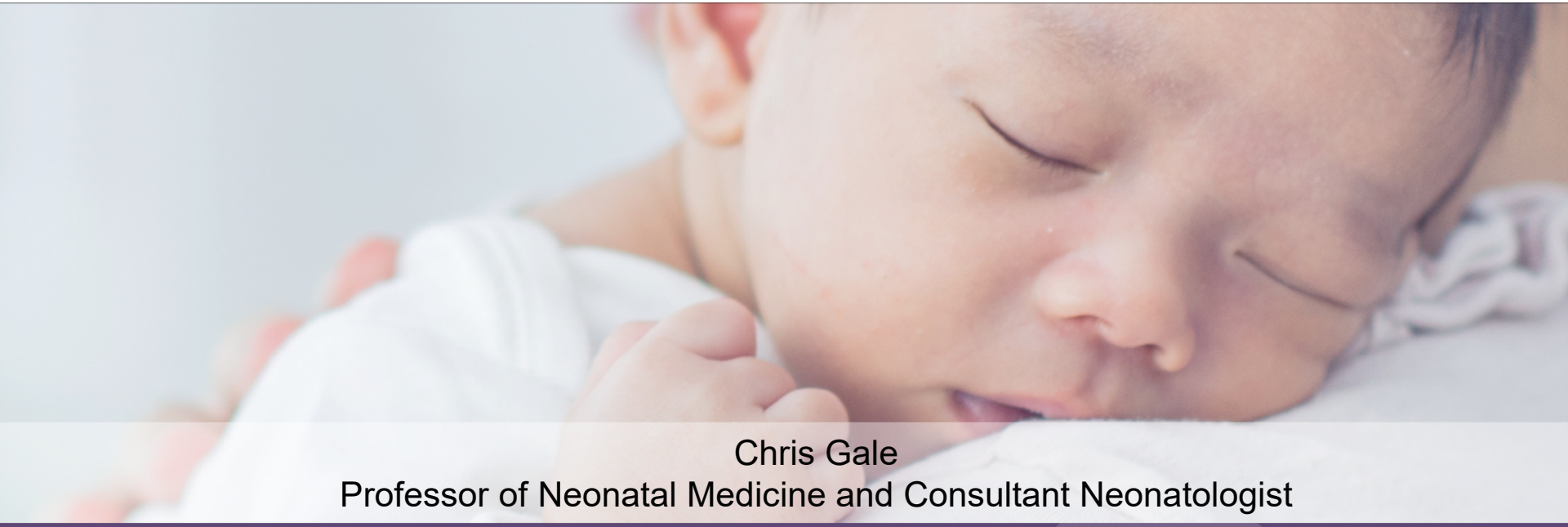

Chris Gale
Professor of Neonatal Medicine and Consultant Neonatologist

The neoGASTRIC trial

What do gastric aspirates tell us about feed tolerance and NEC?

Elizabeth

Michaela

Zoe

CI: Chris Gale, Imperial

Australia: Amy Rodriguez

Australia CI: Calum Roberts Monash

Agenda

- The neoGASTRIC trial
  - Background and Rationale
  - Current Status
- Protocol Highlights
  - Eligibility
  - Randomisation
  - Intervention and Comparator
  - Outcomes
- Questions

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Agenda

- Experience of opt-out consent
- Support for sites
  - Education package
  - Training
- Next steps
- Questions
- Close out

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neoGASTRIC

neoGASTRIC background

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How common is routine measurement in UK?

2018 UK survey of practice

- 95/184 neonatal units
- 40 NICU, 42 LNU
- 59/95 units measured **routinely**
- Only 4 units **did not measure**
- 42/95 (44%) units had guidance
- 30/39: guidance ‘always/usually’ followed

BMJ Paediatrics Open

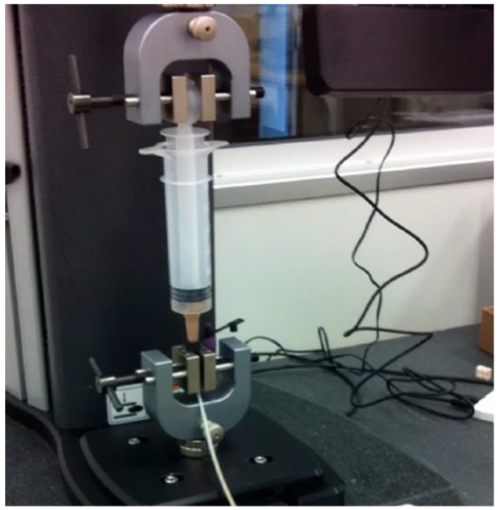
Gastric residual volume measurement in British neonatal intensive care units: a survey of practice

Jon Dorling [1], Lyvonne Tume,[2] Barbara Arch,[3] Kerry Woolfall,[4] Lynne Latten,[5] Louise Roper [4], Elizabeth Deja,[4] Nazima Pathan,[6] Helen Eccleson,[3] Helen Hickey,[3] Michaela Brown,[3] Anne Beissel [7], Izabela Andrzejewska,[8] Frederic Valla,[9] Chris Gale [10]

Table 1 Survey results—GRV practices specific to the management of medical babies (n=90)

Survey question	n (%)
How often do staff in your unit measure GRV?	
Once a day	0 (0)
Before every feed	20 (22.2)
Only when clinically indicated	26 (28.9)
At regular intervals	39 (43.4)
At least every 3, 4 or 6 hours	*35/39*
GRV is not measured	4 (4.4)

What is evidence: is it accurate?



Do gastric aspirates accurately measure gastric contents?

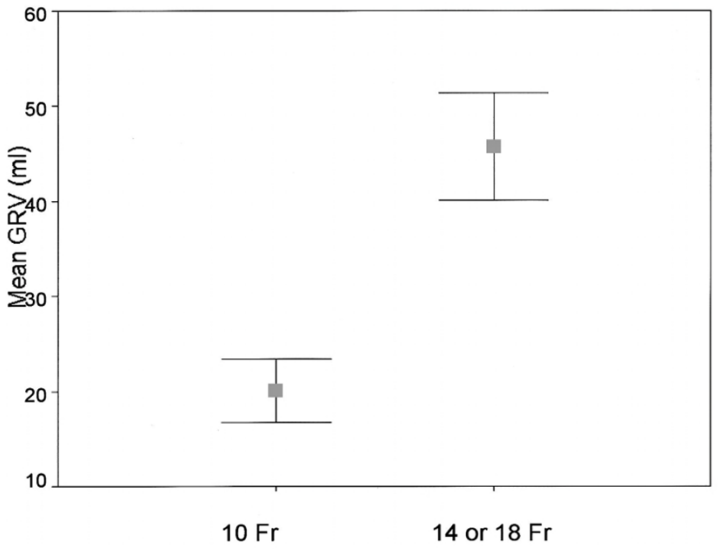
- In vitro study; 10 and 18 Fr adult NG tubes
- Formula: mean 70% aspirated (40-100%)

Influence by infant position

- Higher in supine vs prone

Influenced by NG tube size

- 2-3 times higher with larger tube
- Adult feeding tubes



Not an accurate measure of gastric contents

What is evidence: does it predict NEC?

Small studies looking at gastric aspirates and subsequent NEC

1. NEC (51) vs no NEC (102) **Cobb, Peds 2005**

- Higher aspirates in days before NEC
- Lots of overlap between groups

2. NEC (17) vs no NEC (17) **Bertino, J Peds 2009**

- Higher maximum aspirate before NEC
- More bilious or blood stained aspirates
- 19 days between bloody aspirate and NEC…

Low quality evidence, limited clinical utility

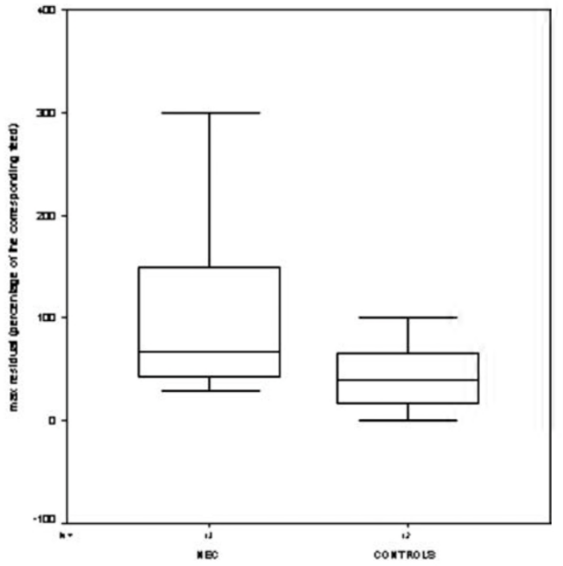


FIG. 1. Maximum residual as percentage of the corresponding feed. Horizontal black bars = median value. Box identifies lower and upper quartile. Whiskers extend from smallest to largest observation.

What about not measuring residuals - RCTs

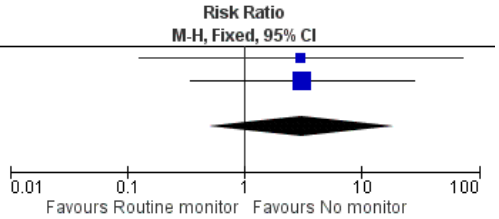
Cochrane review 2019, 2 RCTs Abiramalatha et al.

- Kaur 2016: 80 infants, <1500g BWt; routine GRV vs abdominal girth
- Torazza 2014: 61 infants, 23-31/40; ≤1250g BWt; routine GRV vs no

NEC – Bells 2/3

Study or Subgroup	Routine monitoring Events	Total	No routine monitoring Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaur 2015	1	40	0	40	33.7%	3.00 [0.13, 71.51]
Torrazza 2015	3	30	1	31	66.3%	3.10 [0.34, 28.17]
Total (95% CI)		**70**		**71**	**100.0%**	**3.07 [0.50, 18.77]**
Total events	4		1			

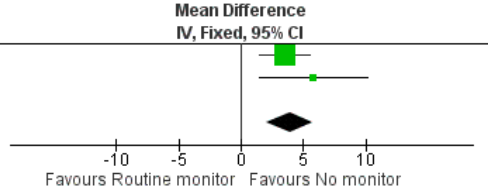
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)



Time to full feeds

Study or Subgroup	Routine monitoring Mean	SD	Total	No routine monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kaur 2015	15.3	5.1	40	11.8	4.2	40	81.9%	3.50 [1.45, 5.55]
Torrazza 2015	28.1	3.9	30	22.3	11.7	31	18.1%	5.80 [1.45, 10.15]
Total (95% CI)			**70**			**71**	**100.0%**	**3.92 [2.06, 5.77]**

Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 4.14 (P < 0.0001)



What about not measuring residuals - RCTs

Parker 2019

- Single centre, USA, 143 babies ≤32/40 and ≤1250g; routine GRV vs no routine GRV
- Time to full feeds (**120**ml/kg/day) **15.9** vs **18.1** days
- Discharged home 8 days earlier in no routine GRV
- NEC (Bells 2/3) – no significant difference

Thomas 2018

- Single centre, India, 104 babies 26-37/40 and BWt 750-2000g; routine GRV vs abdominal girth
- Faster to full feeds in no GRV arm 6 vs 9.5 days; less time in hospital 21 vs 30 days; 1 case of NEC in GRV arm

Small sample size (no data for NEC), limited generalisability

Acceptable trial design – consensus study

Interviews, Delphi, meeting

- 61 neonatal HCPs; 17 parents

Box 1 Final nine outcomes gaining consensus for a trial of no gastric residual volume measurement

- Mortality.
- Incidence of necrotising enterocolitis.
- Time from start of enteral feeding to achieve full (150 mL/kg/day) enteral feeds.
- Days on parenteral nutrition.
- Time feed stopped per 24-hour period.
- Healthcare-associated infections.
- Incidence of catheter-associated blood stream infection.
- Change in weight between birth and neonatal unit discharge.
- Incidence of pneumonia due to milk aspiration.

Most common choice for primary outcome

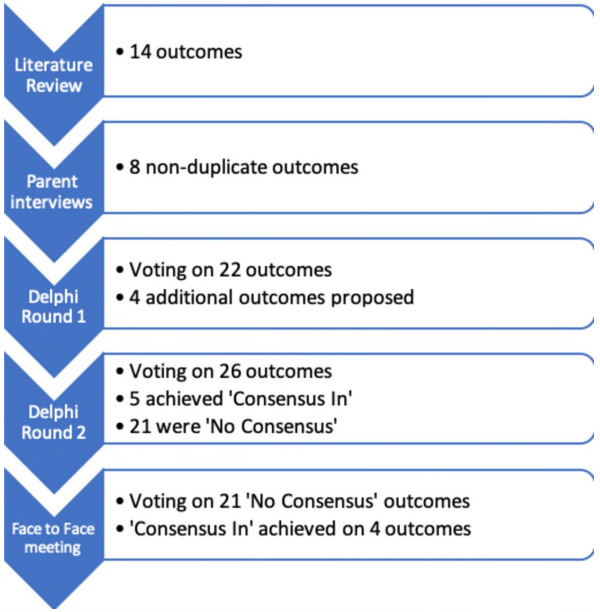
- 24/61 (39%) NEC
- 18/61 (30%) time to full feeds

91% (69/76) would join an RCT

Original research

Optimal outcome measures for a trial of not routinely measuring gastric residual volume in neonatal care: a mixed methods consensus process

Chris Gale [1], Jon Dorling,[2] Barbara Arch,[3] Kerry Woolfall,[4] Elizabeth Deja,[5] Louise Roper [5], Ashley P Jones [6], Lynne Latten,[7] Helen Eccleson,[3] Helen Hickey,[8] Nazima Pathan,[9] Jennifer Preston [10], Anne Beissel [11], Izabela Andrzejewska,[12] Frederic Valla,[13] Lyvonne Tume[14]



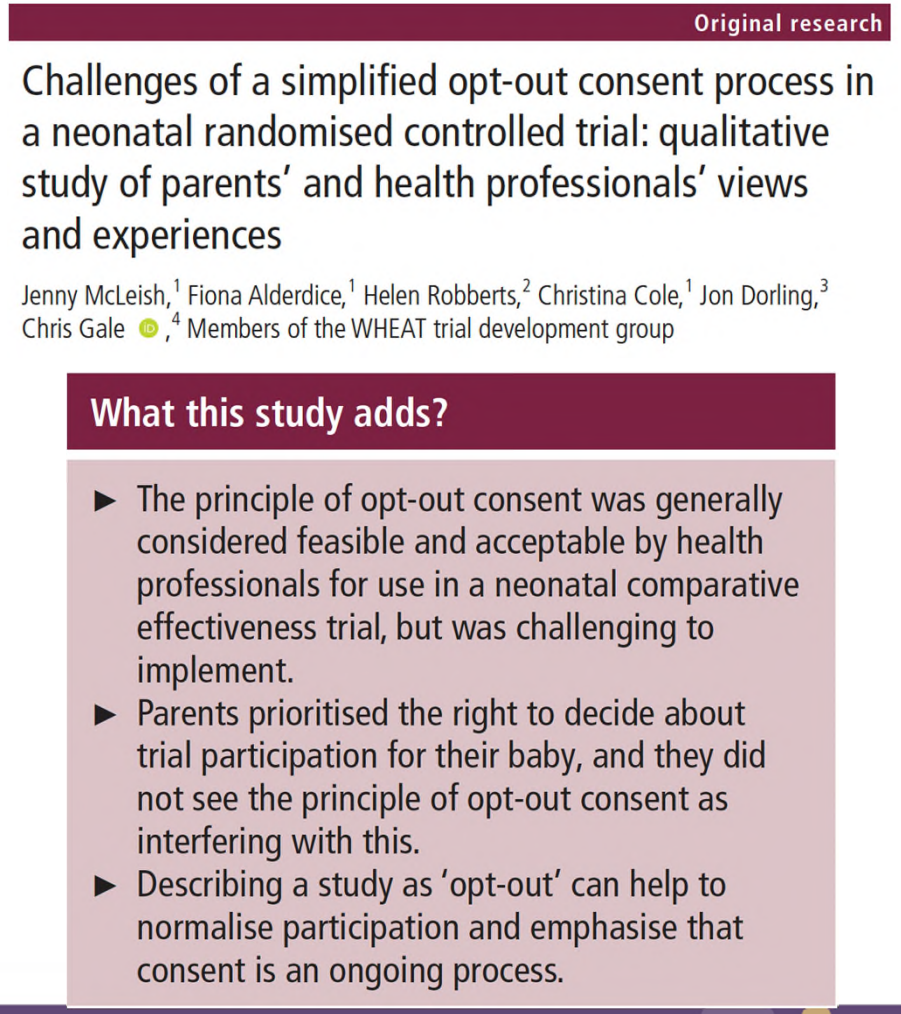
Feasibility of opt-out consent

Qualitative evaluation

- Interviews
- 11 parents; 10 healthcare professionals

Themes

1. Operationalised ‘opt-in’
2. Normalises consent while preserving parent choice
3. Ongoing process of consent
4. No consent forms
5. Wanting ‘normal care’
6. ‘Feeding is better’



Original research

Challenges of a simplified opt-out consent process in a neonatal randomised controlled trial: qualitative study of parents’ and health professionals’ views and experiences

Jenny McLeish,[1] Fiona Alderdice,[1] Helen Robberts,[2] Christina Cole,[1] Jon Dorling,[3] Chris Gale ,[4] Members of the WHEAT trial development group

What this study adds?

- The principle of opt-out consent was generally considered feasible and acceptable by health professionals for use in a neonatal comparative effectiveness trial, but was challenging to implement.
- Parents prioritised the right to decide about trial participation for their baby, and they did not see the principle of opt-out consent as interfering with this.
- Describing a study as ‘opt-out’ can help to normalise participation and emphasise that consent is an ongoing process.

Current Status

UK:

- REC approval Feb 2023
- Local information packs (LIP) sent to 12 sites
  - 4-5 sites close to being ready to start
- REC amendment submitted 4th April 2023
- Open first site May 2023

Australia

- Close to approval
- Open first site May/June 2023

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Protocol Highlights

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Eligibility: Inclusion Criteria

- Gestational age at birth less than 34^{+0} gestational weeks^{+days}
  - (up to and including 33^{+6} gestational weeks^{+days})

- Nasogastric or orogastric tube in place

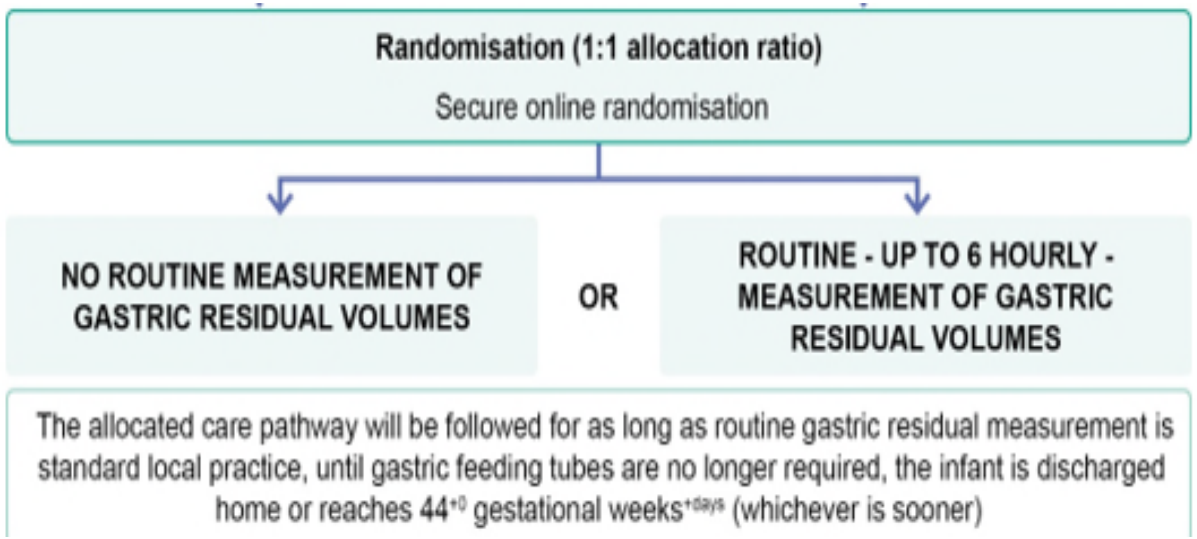
Exclusion Criteria

- Infant has received more than 15 ml/kg/day of milk for more than 24 hours*
- Gastrointestinal surgical condition (including suspected necrotising enterocolitis and focal intestinal perforation) prior to randomisation
- Major congenital abnormalities
- No realistic prospect of survival
- A parent has opted out of infant's participation in neoGASTRIC

*updated in Protocol 2.0

Randomisation

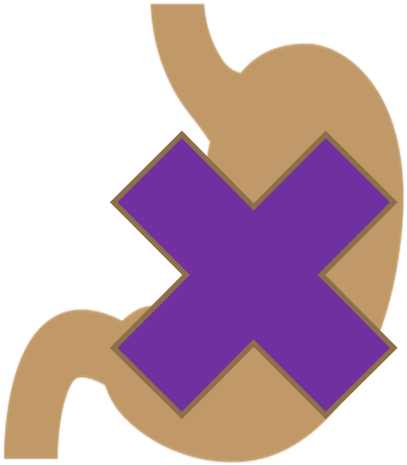
- Randomisation is per infant



Intervention

- Routine Measurement of Gastric Residual Volume

- No Routine measurement of Gastric Residual Volume



What is routine measurement of gastric residual volume?

It is…

- routinely measuring 4-6 hourly to guide enteral feeding
- aspirating whole stomach contents

It is not..

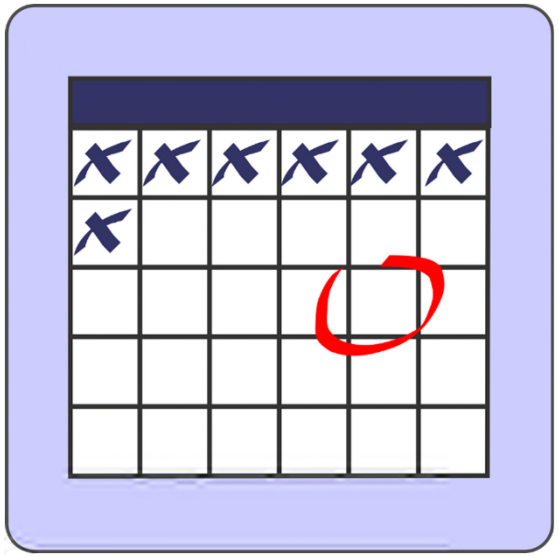
- Aspirating a small amount to confirm feeding tube position, and testing pH

Assessing feed intolerance without using GRV

- Other signs to consider include:
  - Vomiting
  - Abdominal distension / pain / discomfort
  - Bowel movements
    - Appearance of stool
    - Was meconium passed
    - Reduced bowel sounds
  - Metabolic acidosis with lactate >/=2mmol/L

Signs listed above may be caused by other factors so discuss with experienced clinician BEFORE stopping feeds

Objectives



- Primary:
  - Time to full feeds
  - Over 3 consecutive days
- Key secondary:
  - Incidence of NEC
- 23 other secondary outcomes

Secondary outcomes

- Severe necrotising enterocolitis, confirmed at surgery or leading to death
- All-cause mortality
- Focal intestinal perforation
- Gastrointestinal surgery
- Late-onset infection: microbiologically-confirmed (2, 3) or clinically suspected infection (4) >72 hours after birth, evaluated by blinded endpoint review committee
- Duration of neonatal unit stay
- Duration of any parenteral nutrition
- Duration with a central venous line in situ
- Weight standard deviation score
- Head circumference standard deviation score
- Duration of invasive ventilation
- Chronic lung disease

Secondary outcomes

- Retinopathy of prematurity treated medically or surgically
- Brain injury on imaging: intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia (5)*
- Any vomiting resulting in feeds being withheld, up to 14 days from randomisation

* Updated in Protocol 2.0

- Number of days feeds withheld at least once, up to 14 days from randomisation
- Total number of hours feeds withheld, up to 14 days from randomisation
- Breastfeeding at discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner)
- Receiving maternal breastmilk at discharge home or 44^{+0} gestational $weeks^{+days}$ (whichever is sooner)

Secondary outcomes Health Economics

- Number of gastric residual volume measurements
- Abdominal x-ray investigations
- Antibiotic use and surgery for NEC or focal intestinal perforation
- Healthcare costs


Any Questions?

Novel approach of the consent

Automatic enrolment with conditions:

- Information about trial provided to all parents
  - Parent Information Sheet
  - Document action on patient EPR`s and medical paper record
  - Use study eligibility cot card
- Parents can ask for their child not to participate
- Parents can opt-out at any time
- **No signed** consent form (ICF)

This opt-out approach has been the subject of a robust qualitative evaluation involving parents, healthcare professionals and NHS RECs (Arch Dis Child Fetal Neonatal Ed. 2021 May; 106(3): 244–250.)

NIHR | Oxford Health Biomedical Research Centre

About Departments Research Themes COVID-19 Research News & Events Patients

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Opt-out approach to research benefits patients and staff

2nd December 2020

A new study undertaken by an interdisciplinary team at Oxford Health NHS Foundation Trust and the Oxford Health Biomedical Research Centre, has shown that an 'opt-out' approach to research recruitment could benefit both clinical research and patient care.

The study, conducted in three phases across four UK NHS trusts, used focus groups, an appreciative inquiry and online surveys to compare two approaches to discussing research with patients. These included an 'opt-in' approach, where clinicians communicate opportunities to patients, and an 'opt-out' approach where all patients have the right to be informed about research opportunities.

The team's findings showed that 'opt-out' has significant advantages for both patients and researchers. Dr Cathy Henshall, Head of Research Delivery at Oxford Health, who led the project says:

Original research

Challenges of a simplified opt-out consent process in a neonatal randomised controlled trial: qualitative study of parents' and health professionals' views and experiences

Jenny McLeish,[1] Fiona Alderdice,[1] Helen Robberts,[2] Christina Cole,[1] Jon Dorling,[3] Chris Gale ,[4] Members of the WHEAT trial development group

What this study adds?

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- Parents prioritised the right to decide about trial participation for their baby, and they did not see the principle of opt-out consent as interfering with this.
- Describing a study as 'opt-out' can help to normalise participation and emphasise that consent is an ongoing process.

It is all about the communication

OPT OUT CONSENT

Data will be collected and used automatically unless person actively dissents.

BENEFITS

CHALLENGES

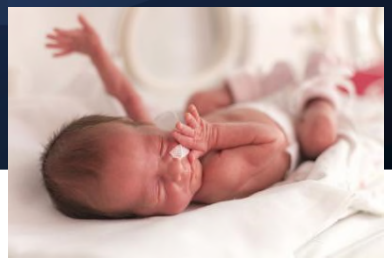
BARRIERS

STANDARDS

OPT – OUT consent online resources

1. An Introduction to the WHEAT Pilot Trial with Chris Gale

2. Current NICU Research and the Waiver of Consent / Opt-Out recruitment process with Melinda Cruz - YouTube

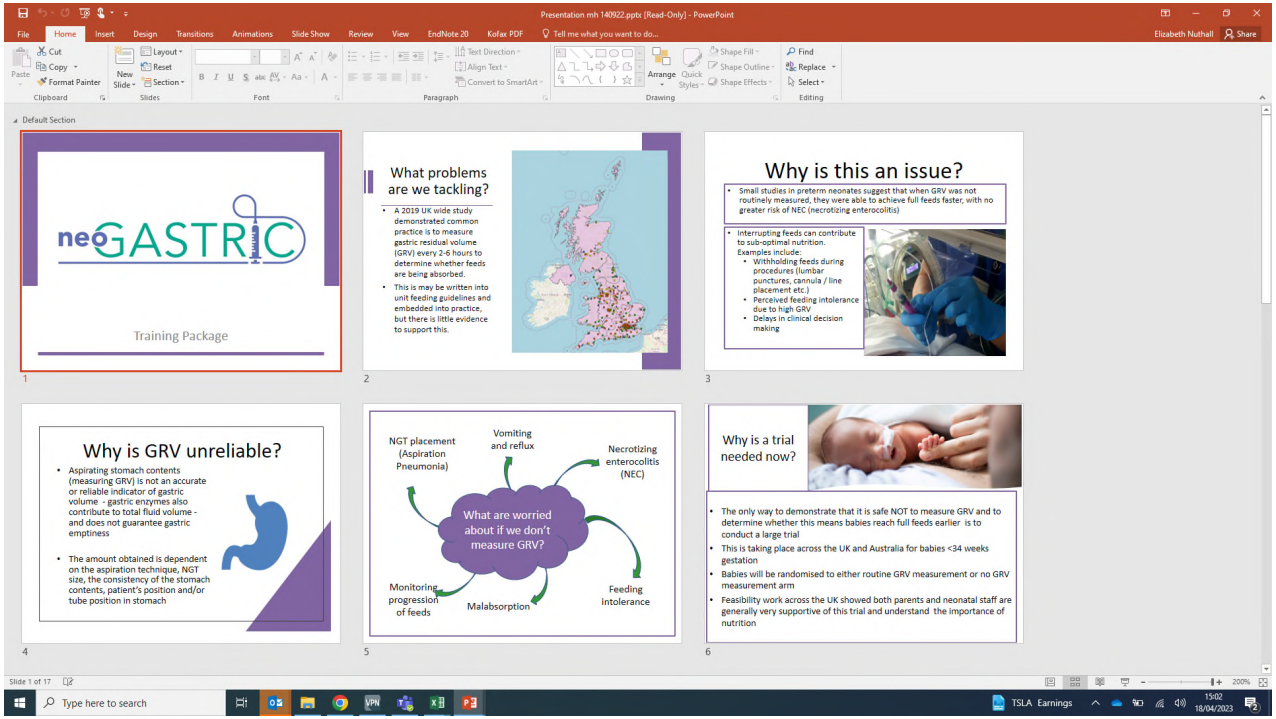


Upcoming neonatal studies with an opt out model

neoGASTRIC

BASE
Bicarbonate for AcidosiS in very pretErm babies

neoGASTRIC education package



Education package

- Available for units to use for staff
- How would units like to use this?
  - Unit lead presentation
  - View recorded presentation
  - Zoom calls for new staff to dial into (e.g. 1/month)
- Any other thoughts?

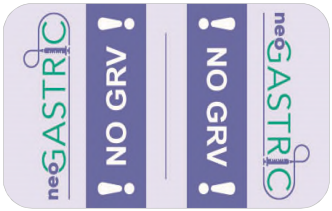
Site training

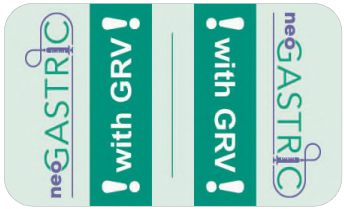
- Site Initiation visit
  - Close to site opening
  - 1/2 day via zoom
- Case Report Form (CRF) training
  - OpenClinica
  - Online
- Randomisation system
  - Online

Site tools

- Cot cards

- Tube labels

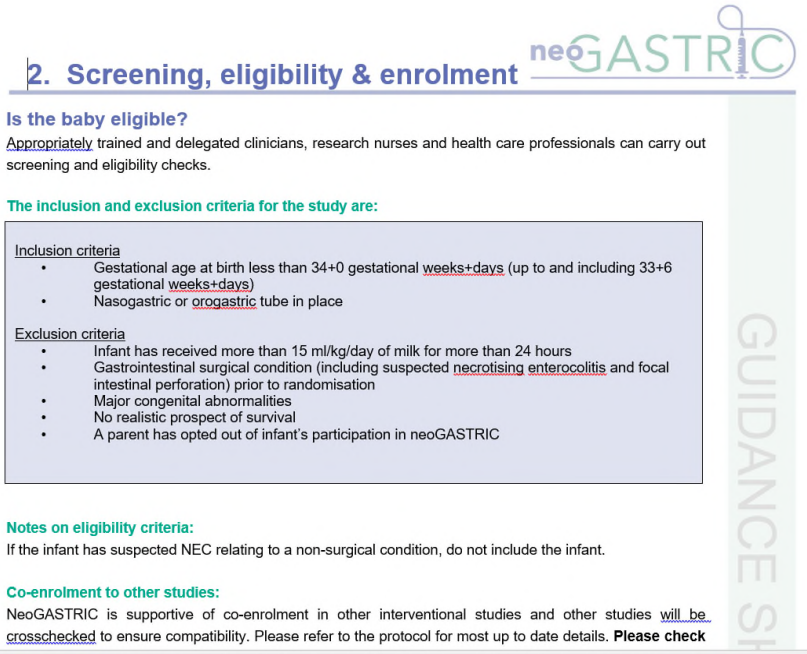




- Stickers

Site tools

- Investigator site file ISF
- Document Box
- Guidance sheets



2. Screening, eligibility & enrolment

Is the baby eligible?

Appropriately trained and delegated clinicians, research nurses and health care professionals can carry out screening and eligibility checks.

The inclusion and exclusion criteria for the study are:

Inclusion criteria

- Gestational age at birth less than 34+0 gestational weeks+days (up to and including 33+6 gestational weeks+days)
- Nasogastric or orogastric tube in place

Exclusion criteria

- Infant has received more than 15 ml/kg/day of milk for more than 24 hours
- Gastrointestinal surgical condition (including suspected necrotising enterocolitis and focal intestinal perforation) prior to randomisation
- Major congenital abnormalities
- No realistic prospect of survival
- A parent has opted out of infant's participation in neoGASTRIC

Notes on eligibility criteria:

If the infant has suspected NEC relating to a non-surgical condition, do not include the infant.

Co-enrolment to other studies:

NeoGASTRIC is supportive of co-enrolment in other interventional studies and other studies will be crosschecked to ensure compatibility. Please refer to the protocol for most up to date details. **Please check**

GUIDANCE SH

- Translated Information sheets
  - 10 languages available
- Website

Next Steps

- If already sent Local Information Pack (LIP)
  - Work with you to progress to SIV and ‘Green light form’
- If not, R+D departments let us know when they are able to receive LIP
- Sites not yet approved
  - Will submit as amendment 2

Next Steps

- Once site is ready:
  - Localise documents
  - Sign Contract
  - Site initiation visit
  - Send eISF and document box
  - Open site
- Get recruiting!

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Elizabeth

Michaela

Zoe

CI: Chris Gale, Imperial

Australia: Amy Rodriguez

Australia CI: Calum Roberts Monash