neoGASTRIC: the largest neonatal trial ever undertaken

neoGASTRIC - a multicentre randomised control trial in the UK and Australia looking at whether the routine measurement of gastric residual volumes is good or bad for preterm babies.

neoGASTRIC

Imperial College London

FUNDED BY NIHR | National Institute for Health and Care Research

Monash Newborn
Handled with Care

MONASH University

Australian Government
National Health and Medical Research Council

NPEU
Clinical Trials Unit

OXFORD POPULATION HEALTH
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Agenda

- The neoGASTRIC trial and protocol highlights
- Common questions
- Experience so far…
- Questions

Summary of existing evidence

Routine measurement of GRV is ubiquitous

- Probably inaccurate measure of gastric contents
- 4 small, single centre trials – consistently show not measuring GRV leads to earlier full feeds
- Not generalisable to UK (India or USA)
- May also reduce hospital stay
- Underpowered to examine NEC

Remains embedded in UK practice

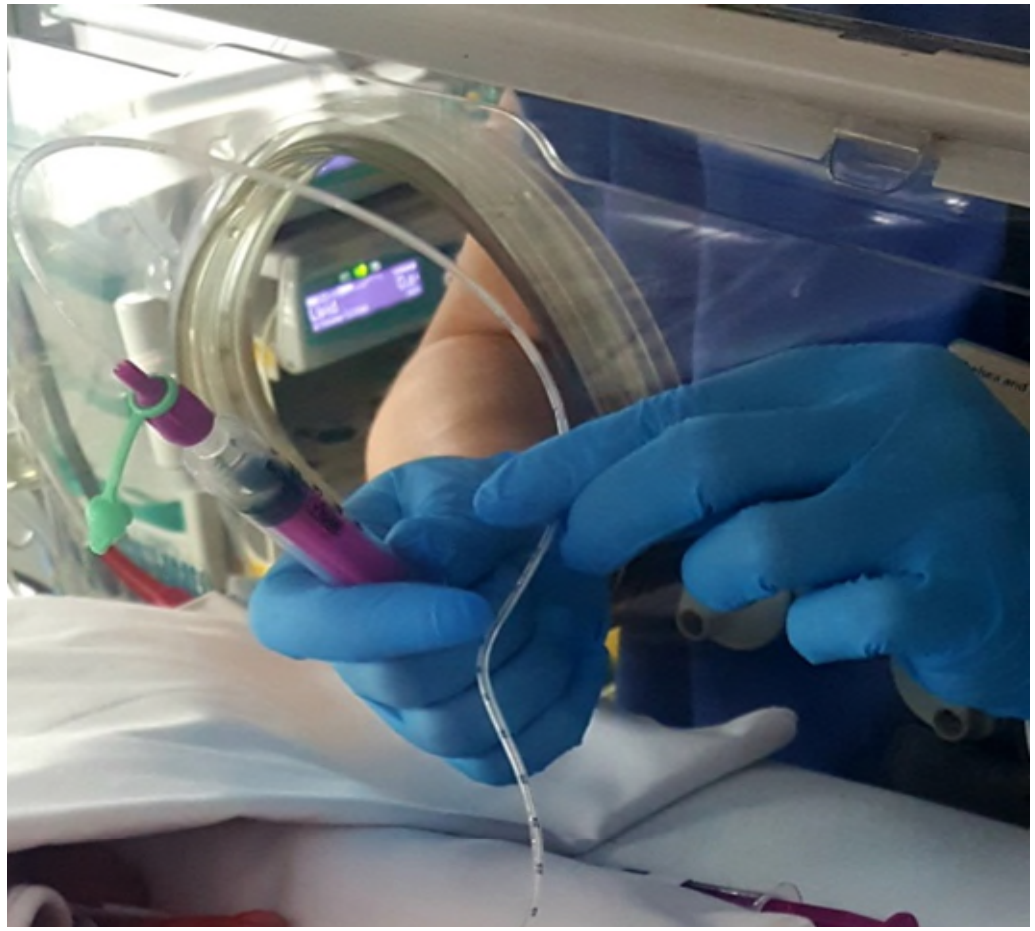
The neoGASTRIC trial

P Among babies born <34+0 gestational weeks

I Does no routine measurement of gastric residual volume

C Compared to routine (up to 6 hourly) measurement of gastric residual volumes

O Lead to faster establishment of full enteral feeds without increase in NEC?



What are gastric residuals?

- Aspiration of the whole stomach contents
- Usually before feeds are given
- Assess volume and colour
- Assess for ‘feed intolerance’
- Prevent vomiting/aspiration?
- Early identification/prevention of necrotising enterocolitis?
- **NOT: aspirating a small amount to confirm naso-gastric tube position**

The neoGASTRIC Trial

Individually randomised, unblinded, parallel arm, comparative effectiveness trial

- Both comparator arms are used as standard of care in the UK

United Kingdom and Australia

Opt-out consent

Embedded process evaluation

Study Within A Trial (SWAT)

Timeline

- Recruitment June 2023-2026

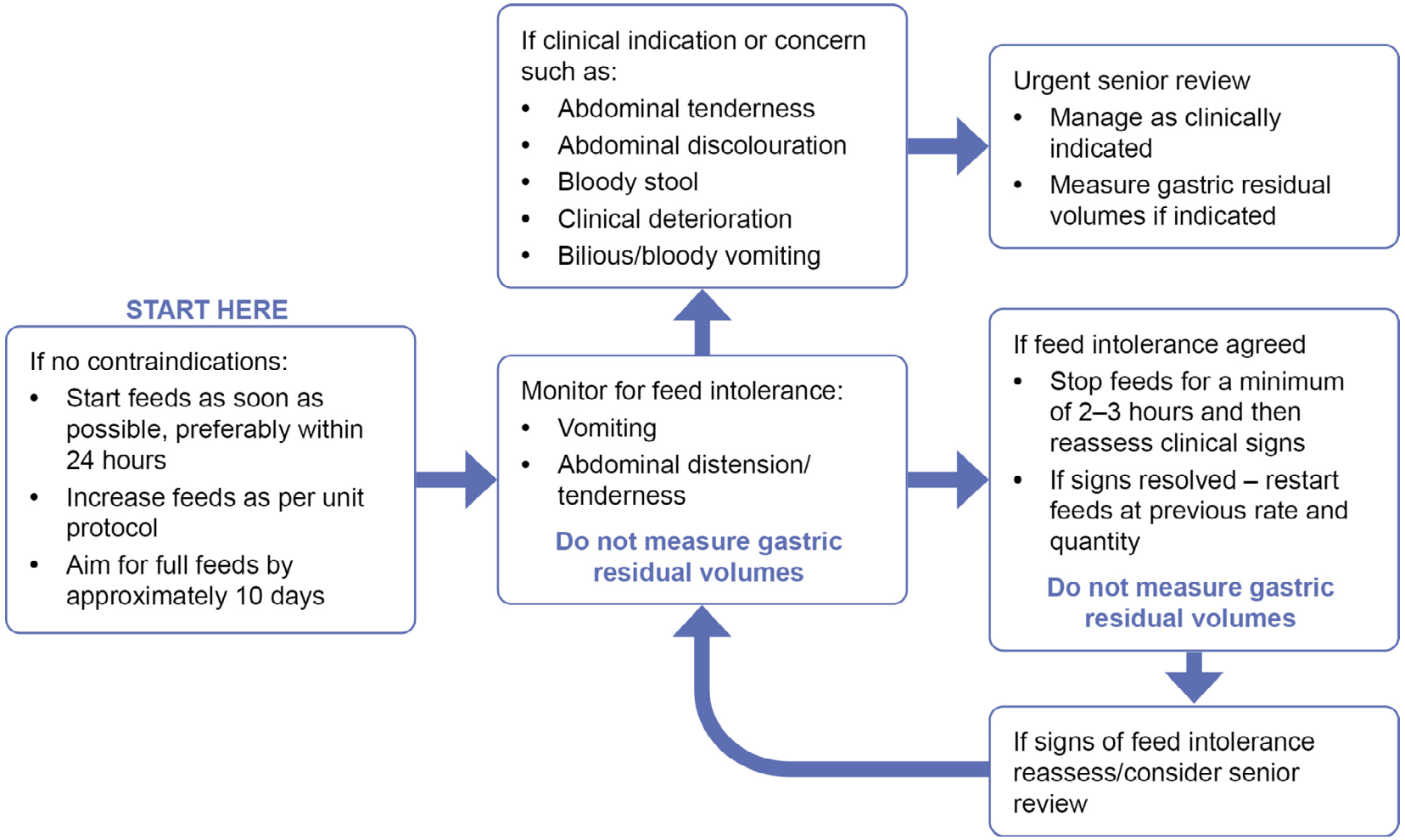
Inclusion criteria

- Preterm birth <34+0 gestational weeks
- Nasogastric/orogastric tube in place

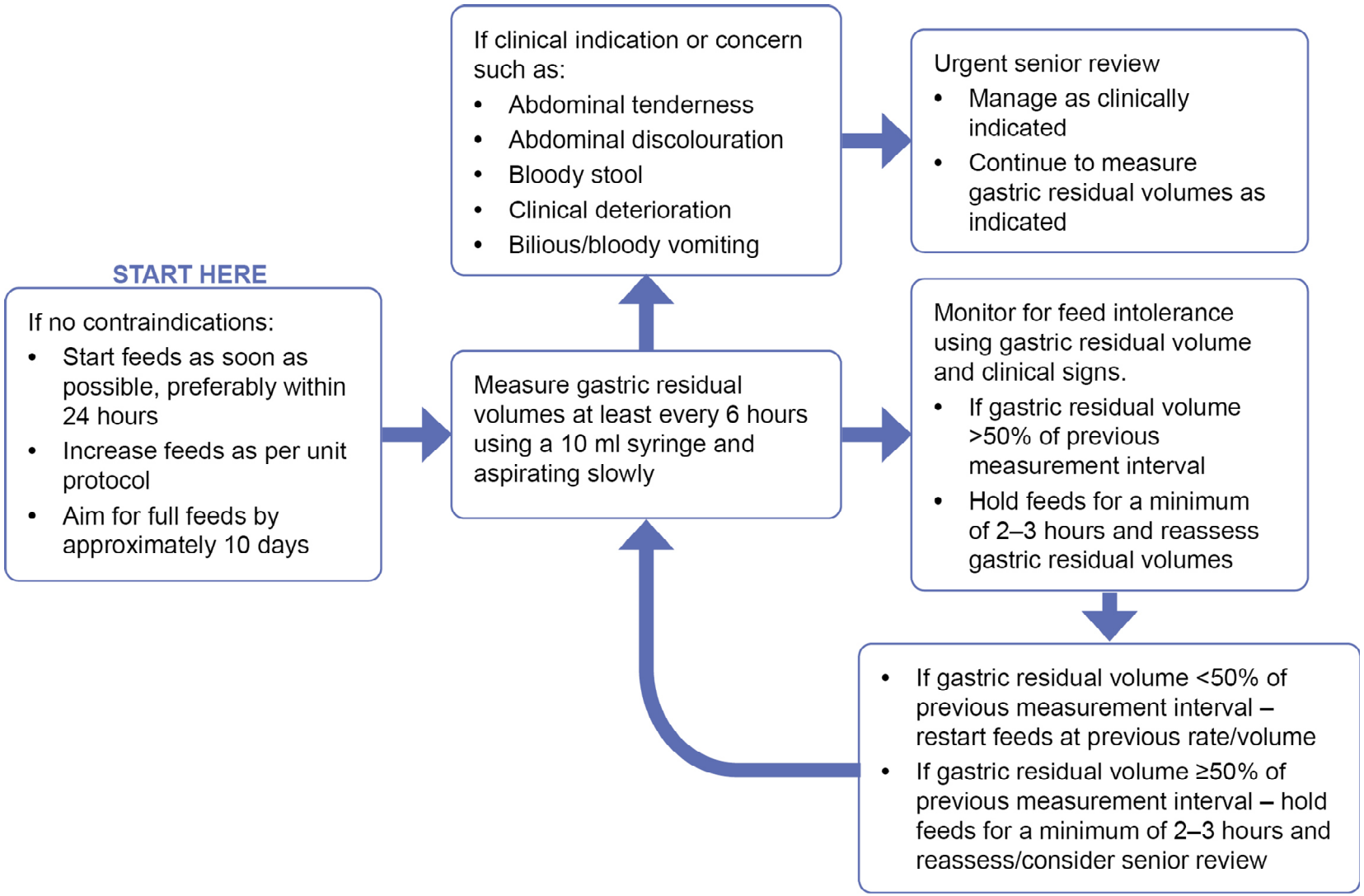
Exclusion criteria

- **Infant has received more than 15 ml/kg/day of milk for more than 24 hours**
- Gastrointestinal surgical condition
- Major congenital abnormality
- Unlikely to survive
- Parent has opted out

Suggested intervention arm (pragmatic)



Suggested control arm (or local practice)



Outcomes

Primary (superiority)

- Time to reach full milk feeds for 3 consecutive days (145ml/kg/day)

Key secondary (non-inferiority)

- Necrotising enterocolitis

Secondary (superiority)

- All cause mortality
- Focal intestinal perforation
- Gastrointestinal surgery
- Late onset infection
- Duration of neonatal unit stay
- Duration of PN
- Duration of central line in-situ
- Growth
- Duration of ventilation
- Chronic lung disease
- Retinopathy of prematurity
- Vomiting interrupting feeds
- Number of feeds withheld
- Breastfeeding at discharge

Sample size…

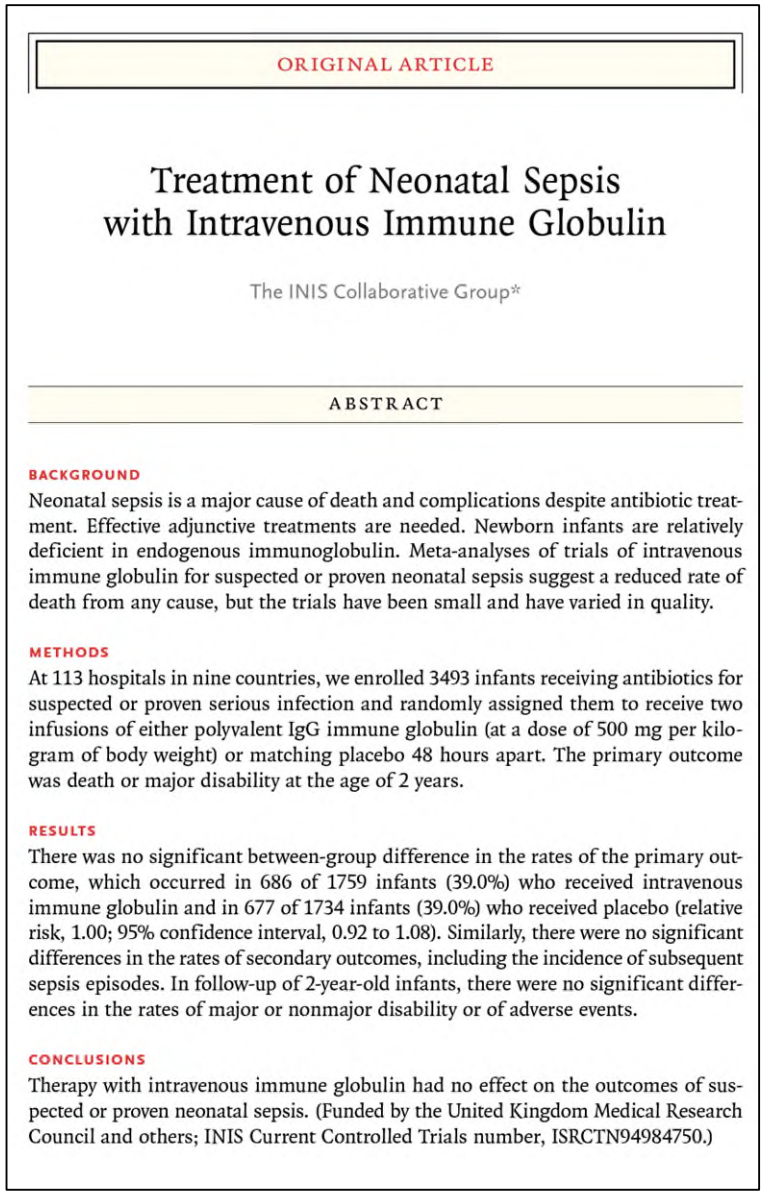
Time to full feeds

- Background mean (SD) for <34/40 babies: 9.4 (10.8) days
- To detect 1 day reduction in time to full feeds (90% power, 5% significance)
- **7040 babies – 3520 per arm**
- ~13,000/yr live births <34/40 in UK (1500/yr in Victoria, >5000/yr Aus)

Necrotising enterocolitis

- Background rate <34/40 is 3%
- 7040 babies: 92% power to detect non-inferiority margin of 1.6% (1-sided 2.5% significance)

Well powered for length of stay, duration of PN



ORIGINAL ARTICLE

Treatment of Neonatal Sepsis with Intravenous Immune Globulin

The INIS Collaborative Group*

ABSTRACT

BACKGROUND

Neonatal sepsis is a major cause of death and complications despite antibiotic treatment. Effective adjunctive treatments are needed. Newborn infants are relatively deficient in endogenous immunoglobulin. Meta-analyses of trials of intravenous immune globulin for suspected or proven neonatal sepsis suggest a reduced rate of death from any cause, but the trials have been small and have varied in quality.

METHODS

At 113 hospitals in nine countries, we enrolled 3493 infants receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years.

RESULTS

There was no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or nonmajor disability or of adverse events.

CONCLUSIONS

Therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis. (Funded by the United Kingdom Medical Research Council and others; INIS Current Controlled Trials number, ISRCTN94984750.)

How do we recruit 7000 babies?

Simplified, opt-out consent

1. Information displayed on unit
2. A simple 2-sided information sheet
3. Information translated in 10 languages
4. Animation explaining trial
5. Can ask for their baby not to participate
6. Participation as the norm
7. Can opt-out at any time
8. No signed consent form

Qualitative evaluation

- Interviews: 11 parents; 10 healthcare professionals

Themes

- Normalises consent while preserving parent choice
- Ongoing process of consent
- Preferred no consent forms

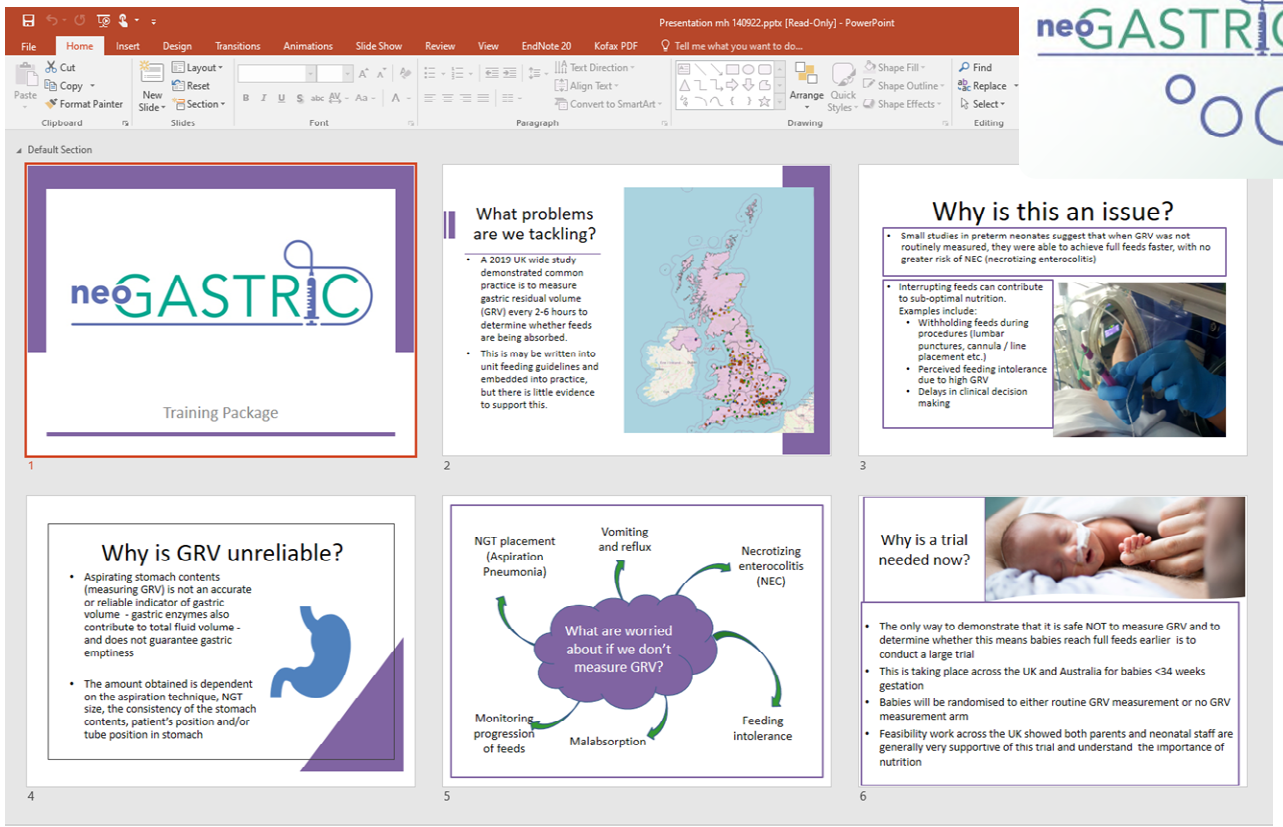

Original research

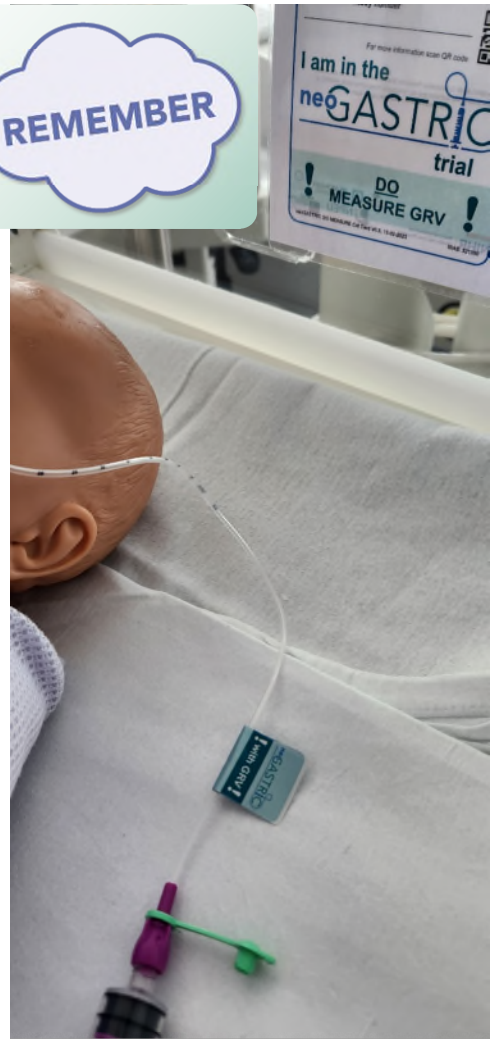
Challenges of a simplified opt-out consent process in a neonatal randomised controlled trial: qualitative study of parents' and health professionals' views and experiences

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

Trial animation

Education and training materials



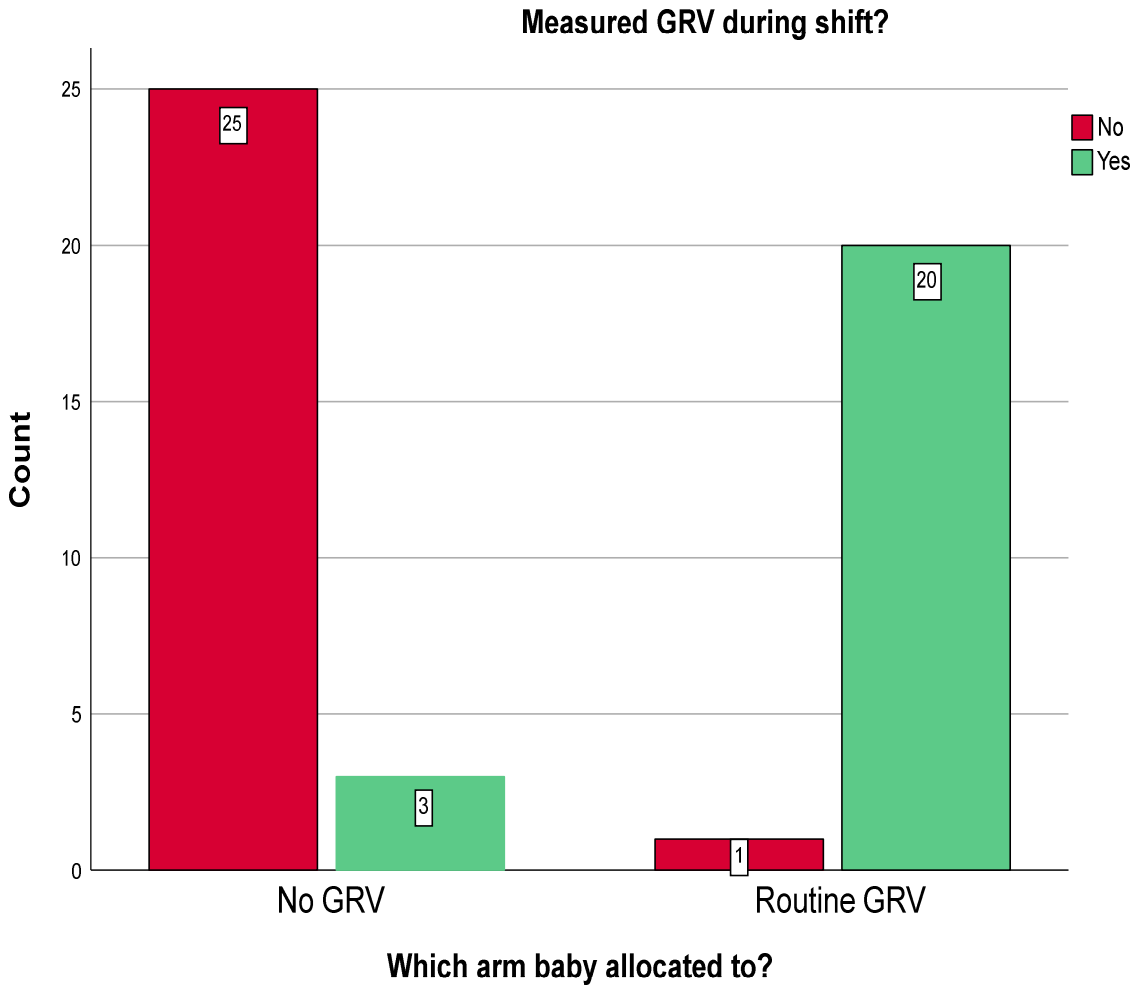


Embedded process evaluation

Observation, interviews – 4 units

Insight from parents

- Challenges do not appear related to not measuring gastric residuals
- 4 (including triplets) “I opted out initially but after more information, I was happy to continue”
- Timing of approach?
- “I opted out because I didn't want to participate and I want my babies information confidential in every way.”



Study within a trial

P: Parents eligible for neoGASTRIC trial

I: Trial information on a hand-held digital multimedia and written information leaflet

C: Trial information on a written information leaflet

O: Recruitment into neoGASTRIC trial

- Cluster randomisation at level of neonatal unit
- 36 neonatal units

Current Status

UK:

- 1st site opened June 2023
- 17 (of 40) units open to recruitment

Australia

- 1st site opened June 2023
- 2 units (of 4) open to recruitment

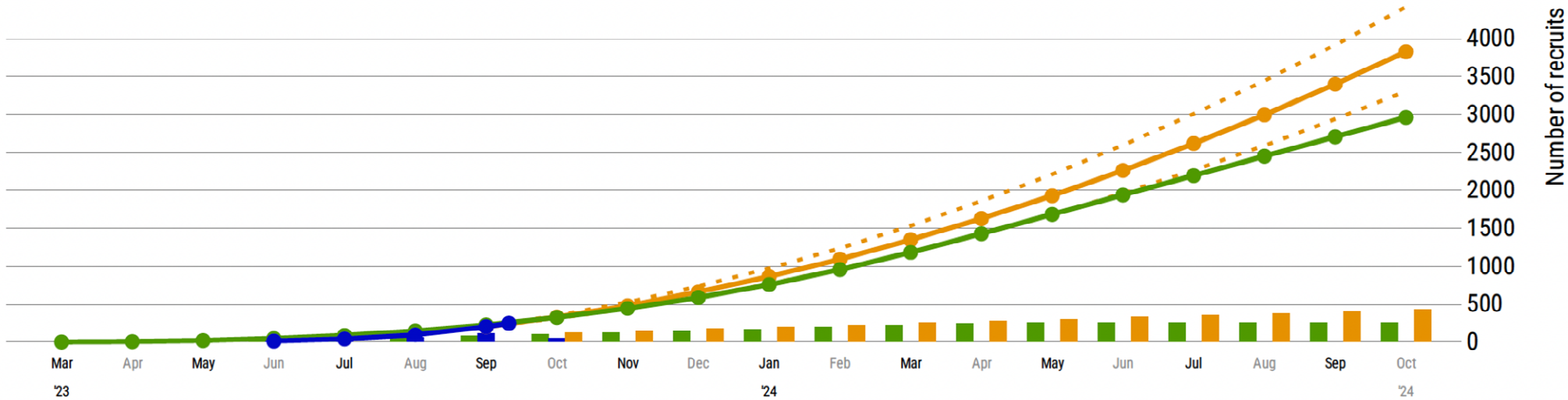
Total recruitment = 346

The neoGASTRIC trial – recruitment

Recruitment Summary						
Recruiting centre	Total	Oct 23	Sep 23	Aug 23	Jul 23	Jun 23
Arrowe Park Hospital, Wirral	3	3	0	0	0	0
Hull Royal Infirmary	15	7	8	0	0	0
Jessop Wing, Sheffield	28	17	11	0	0	0
John Radcliffe Hospital, Oxford	14	6	8	0	0	0
Liverpool Women's Hospital	53	18	19	16	0	0
Monash Children's Hospital, Monash	50	11	12	7	12	8
Northwick Park Hospital, Harrow	6	3	3	0	0	0
Peterborough City Hospital	10	7	3	0	0	0
Prince Charles Hospital, Merthyr Tydfil	0	0	0	0	0	0
Princess Anne Hospital, Southampton	37	9	10	12	6	0
Queen Alexandra Hospital, Portsmouth	25	11	14	0	0	0
Royal Cornwall Hospital (Treliske)	14	3	3	2	2	4
Saint Mary's Hospital, Manchester	29	15	4	7	3	0
Singleton Hospital, Swansea	22	10	7	5	0	0
St George's Hospital, London	1	1	0	0	0	0
The Royal Women's Hospital, Parkville	7	7	0	0	0	0
University Hospital of North Tees	9	6	0	3	0	0
Watford General Hospital	18	4	6	3	5	0
William Harvey Hospital, Ashford	5	5	0	0	0	0
	346	**143**	**108**	**55**	**28**	**12**

Target, actual & projected recruitment, projected for 12 months

Monthly recruitment: Target Actual Projected | **Cumulative:** Target Actual Projected Projected CI ± 95%



	Mar '23	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan '24	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct '24
Target monthly recruitment	0	5	14	28	42	59	78	99	120	144	170	198	226	246	255	255	255	255	255	255
Actual monthly recruitment				12	28	55	108	45												
Projected monthly recruitment								128	151	181	204	226	256	279	302	332	354	377	407	430
Target cumulative total	0	5	19	47	89	148	226	325	445	589	759	957	1183	1429	1684	1939	2194	2449	2704	2959
Actual cumulative total				12	40	95	203	248												
% target				26	45	64	90	76												
Projected total 95% CI lower							203	313	442	596	770	964	1183	1422	1679	1963	2266	2588	2937	3304
Projected cumulative total							203	331	482	663	866	1092	1349	1628	1929	2261	2615	2992	3399	3829
Projected total 95% CI upper							203	352	527	737	974	1237	1534	1859	2209	2594	3006	3444	3917	4416

Common questions

When to enrol babies?

- Exclusion criteria:

  Infant has received more than 15 ml/kg/day of milk for more than 24 hours

- All babies can be included in first 24 hours regardless of feed volume
  - as they will have received it for less than 24 hours
- Those babies that have a period of ‘trophic’ feeds can be randomised until they have had 24 hours on more than trophic feeds.

What to measure before and after full feeds

- In no measurement arm
  - OK if clinical indication or concern
  - Mark on feed log
- In measurement arm
  - OK not to measure when establishing oral feeds
- After full feeds reached
  - Prefer to stay on allocated arm of trial
  - Unless local protocol indicates otherwise

Feed logs

- On day 0, which is the day of randomisation
  - complete the daily feed log for the whole 24 hour period
  - irrespective of the time of day the baby was randomised
- Complete the feeding log for each calendar day (24 hours from 00:00)
- Feeds withheld
  - We want to know how long feeds were held for any reason (including for aspirates)
  - but specifically we want to know about feeds withheld for vomiting as it is a separate outcome
  - in the first 14 days only

Feed logs

- Serious Clinical Concerns?
  - What does this mean?
  - Changing protocol to ‘Clinical indication or concern’

Screening logs

- Please complete on the randomisation system at least once per month
- Important for the SWAT
  - Seeing if a short video pre-loaded on a tablet given to parents makes a difference in recruitment

Sites managing multiple studies

- How do parents feel about recruiting into multiple studies?

Experience so far…

- How to ensure staff stay on the right arm of the trial?
- Opt-out consent – how is it working?
- Any tips for new units?

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