Clinical trial results:
Delivering adequate nutrition to critically ill patients suffering delayed gastric emptying: RCT of nasointestinal feeding versus nasogastric feeding plus prokinetics.

Summary

EudraCT number	2012-001374-29
Trial protocol	GB
Global end of trial date	12 May 2014

Results information

Result version number	v1 (current)
This version publication date	30 April 2021
First version publication date	30 April 2021

Trial information

Trial identification

Sponsor protocol code	1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Reference: 2787

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Level 3, Learning & Research building, Bristol, United Kingdom, BS10 5NB
Public contact	Taylor, Stephen, +44 01173406581, stephen.taylor@nbt.nhs.uk
Scientific contact	Taylor, Stephen, +44 01173406581, stephen.taylor@nbt.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2014
Global end of trial reached?	Yes
Global end of trial date	12 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Delayed gastric emptying (DGE) commonly limits the use of enteral nutrition (EN) and may increase ventilator-associated pneumonia. Nasointestinal feeding has not been tested against dual prokinetic treatment (Metoclopramide and Erythromycin) in DGE refractory to metoclopramide. This trial tests the feasibility of recruiting this 'treatment-failed' population and the proof of concept that asointestinal (NI) feeding can increase the amount of feed tolerated (% goal) when compared to nasogastric (NG) feeding plus metoclopramide and erythromycin treatment.

Protection of trial subjects:

Because critically ill patients cannot initially consent to treatment we asked their legally authorised representative
(relatives or clinician) to give consent then ask patients to consent to stay in the study, if and when they were able to do so.

Nasointestinal feeding necessitates placement of an additional tube. A guidance system was used to track placement in realtime, permitting tube withdrawal to prevent serious misplacement or trauma .

Background therapy:

All patients received the best standard treatment regardless of whether they were in the study.

Evidence for comparator:

The prokinetic group received continued treatment with metolcopramide in addition to treatment with erythromycin. Both drugs are routinely used as a prokinetic drugs in clinical practise.

Actual start date of recruitment	03 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study ran from 22/02/2013 to 12/05/2014 including 5 days follow up.

Pre-assignment

Screening details:

Eligible patients were those who were mechanically ventilated and over 20 years old, with delayed gastric emptying (DGE). 1115 participants were screened. Of 208 patients with DGE, 77 were eligible, 2 refused assent, 25 had contraindications to intervention,
almost exclusively prokinetic treatment, and it was feasible to recruit 50.

Period 1

Period 1 title	treatment allocation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Intervention blinding was not possible because the of the requirement to use enteral tubes

Arms

Are arms mutually exclusive?	Yes
Arm title	NG Feed, metoclopramide and erythromycin

Arm description:

NG Feed, metoclopramide & erythromycin 250mg IV 4x/d

Arm type	Active comparator
Investigational medicinal product name	Metoclopramide
Investigational medicinal product code	CAS number; 7232-21-5 IMP no. PR3
Other name	Maxolon
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Discontinued 48h after gastric emptying adequate. 10mg per day. Total dose 30mg. Full Molecular formula: 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxybenzamide.

Investigational medicinal product name	Erythromycin
Investigational medicinal product code	CAS Number; 3847-29-8 IMP No. PR3
Other name	n/a
Pharmaceutical forms	Injection
Routes of administration	Intravenous drip use

Dosage and administration details:

Maximum 250mg per day. Total dose 1000mg.
Full Molecular formula; 4-(dimethylamino)-3-hydroxy-6-methyloxan2-y-l]oxy}-14-ethyl-7, 1 2, 13-trihydroxy-4-{[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4, 6-dimet hyloxan-2-yl]oxy}-3,5,7,9,11,13-hexamethy-1-oxacyclotetradecan e-2,10-dione C37H67NO13

Arm title	EM-Guided NI Tube & Feeding, Stop Prokinetics

Arm description:

EM-guided NI tube & feeding, stop prokinetics

Arm type	Alternative Treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	NG Feed, metoclopramide and erythromycin	EM-Guided NI Tube & Feeding, Stop Prokinetics
Started	25	25
Completed	24	25
Not completed	1	0
Physician decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	NG Feed, metoclopramide and erythromycin
Reporting group description: NG Feed, metoclopramide & erythromycin 250mg IV 4x/d	
Reporting group title	EM-Guided NI Tube & Feeding, Stop Prokinetics
Reporting group description: EM-guided NI tube & feeding, stop prokinetics	

Reporting group values	NG Feed, metoclopramide and erythromycin	EM-Guided NI Tube & Feeding, Stop Prokinetics	Total
Number of subjects	25	25	50
Age categorical Units: Subjects			
Age continuous Units: years			
median	51	53	
inter-quartile range (Q1-Q3)	36 to 59	42 to 61	-
Gender categorical Units: Subjects			
Female	7	5	12
Male	18	20	38
Not Recorded	0	0	0
Category			
Disease Category			
Units: Subjects			
Medical	7	9	16
Neurosurgery (Non-Trauma)	9	6	15
Surgery (Abdominal)	3	4	7
Trauma	6	6	12
Not Recorded	0	0	0
APACHE II Score Units: Score			
median	16	18	
inter-quartile range (Q1-Q3)	13 to 19	12 to 24	-
Height Measured (cm) Units: centimetres			
median	178	173	
inter-quartile range (Q1-Q3)	166 to 180	171 to 180	-
Weight estimate (kg) Units: Kilograms			
median	80	75	
inter-quartile range (Q1-Q3)	73 to 110	70 to 80	-

End points

End points reporting groups

Reporting group title	NG Feed, metoclopramide and erythromycin
Reporting group description: NG Feed, metoclopramide & erythromycin 250mg IV 4x/d	
Reporting group title	EM-Guided NI Tube & Feeding, Stop Prokinetics
Reporting group description: EM-guided NI tube & feeding, stop prokinetics	

Primary: Feed Goal Tolerated

End point title	Feed Goal Tolerated
End point description: All patients were increased from 40 mL feed/h or current rate to full rate whenever tolerated. Tolerance was defined GRVs <250 mL and no vomiting in the prokinetic group and where GRVs contained no macroscopic feed in the NI group. The first GRV 250 mL was discarded and EN was continued at the same rate but a second consecutive 4 hourly GRV 250 mL was discarded and the feed rate was reduced 50%. Ileus triggered cessation of EN and 4 hourly re-assessment for risk of bowel ischaemia.	
End point type	Primary
End point timeframe: Over the 5 days of the intervention or up to the point of death.	

End point values	NG Feed, metoclopramide and erythromycin	EM-Guided NI Tube & Feeding, Stop Prokinetics		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage				
Day -2	29	35		
Day -1	23	0		
Day 1	50	87		
Day 2	80	88		
Day 3	89	94		
Day 4	60	94		
Day 5	72	95		

Statistical analyses

Statistical analysis title	% Feed Goal Tolerated between groups
Statistical analysis description: ‘blind to intervention’, intention-to- treat analyses. Normality was determined by a ShapiroeWilks test (p<0.05) and an independent samples Student's t test or ManneWhitney test as appropriate. The 95% confidence intervals (95%CI) refer to the mean or median difference between treatment groups in the respective tests. Categorical data was analysed using Fisher's exact test.	
Comparison groups	EM-Guided NI Tube & Feeding, Stop Prokinetics v NG Feed,

	metoclopramide and erythromycin
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.026 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Effect sizes ([mean of intervention e control]/ standard deviation) and bootstrapped 95%CI for medians were
calculated and presented with the percentage difference between intervention and control. Analyses for continuous and categoricalvariables were done using Cohen's d and Cramer's V tests, respectively. A ManneWhitney test was used to determine the difference of the area under the curves of feed goal (%), to provide an overall pvalue over the 5 days of the intervention or up to death.

[2] - (Median [IQR] 432 [253-464]% vs. 350 [213-381]%)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 22/05/2013 - 12/05/2014	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	NG Feed, metoclopramide and erythromycin
Reporting group description: -	
Reporting group title	EM-Guided NI Tube & Feeding, Stop Prokinetics
Reporting group description: -	

Serious adverse events	NG Feed, metoclopramide and erythromycin	EM-Guided NI Tube & Feeding, Stop Prokinetics	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 24 (29.17%)	6 / 25 (24.00%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	4 / 24 (16.67%)	4 / 25 (16.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 24 (4.17%)	3 / 25 (12.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
systemic candidiasis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventilator-associated pneumonia			

subjects affected / exposed	4 / 24 (16.67%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Tachycardia	Additional description: Tachycardia, ectopics, loss of output: Erythromycin stopped		
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Liver function test increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NG Feed, metoclopramide and erythromycin	EM-Guided NI Tube & Feeding, Stop Prokinetics	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 24 (37.50%)	8 / 25 (32.00%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 24 (8.33%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Gastric Distension			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	5 / 24 (20.83%)	3 / 25 (12.00%)	
occurrences (all)	20	4	
Ileus	Additional description: Erythromycin stopped		

subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Product issues			
Rash	Additional description: Erythromycin stopped		
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Renal replacement therapy			
subjects affected / exposed	0 / 24 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Hypernatraemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations of this study include inability to perform ‘intervention blinding’ or quantify gastric emptying, introducing potential
bias and reducing the efficacy in recruiting the target group, respectively.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28531392