Clinical trial results:
The efficacy of Indwelling Pleural Catheter placement versus IPC placement PLUS sclerosant (talc) in patients with malignant pleural effusions managed exclusively as out-patients

Summary

EudraCT number	2012-000599-40
Trial protocol	GB
Global end of trial date	09 December 2016

Results information

Result version number	v1 (current)
This version publication date	12 May 2018
First version publication date	12 May 2018
Summary attachment (see zip file)	supplementary material for publication (IPC-Plus appendix - revised3.pdf) protocols and analysis plans (Protocol and analysis plans - revised.pdf) IPC-Plus NEJM paper (NEJMoa1716883.pdf)

Trial information

Trial identification

Sponsor protocol code	2795

Additional study identifiers

ISRCTN number	ISRCTN73255764
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Southmead Hospital, Bristol, United Kingdom,
Public contact	Trial manager, Respiratory Research, North Bristol NHS Trust, emma.keenan@nbt.nhs.uk
Scientific contact	Trial coordinator, Academic Respiratory Unit, University of Bristol, rahul.bhatnagar@bristol.ac.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	09 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2016
Global end of trial reached?	Yes
Global end of trial date	09 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The IPC-PLUS trial is a study to help determine the best way to manage patients who develop fluid around the lung as a result of cancer (malignant pleural effusion). The aim is to compare outcomes in two groups of patients. The first group will be treated with an indwelling pleural catheter (IPC, or tunnelled chest tube) to help drain away the fluid, and will then be given an inert placebo substance (saline) into the drain before being followed up. The second group will receive the same type of IPC to drain away the fluid, but will then be given an injection of sterile talc powder into the drain instead of placebo. Our primary objective is to determine whether introducing talc through the IPC leads to an improved rate of successful pleurodesis, whereby the two linings of the lung are stuck together to prevent further fluid build-up. This is a randomised controlled trial, which means patients will be randomly allocated to receive either the placebo injection or the talc injection

Protection of trial subjects:

The study was reviewed and approved by an approved NHS ethics committee and by the MHRA
Patients were seen on a frequent basis (every 2 weeks)
An emergency phone number was provided to all participants and was available at all times

Background therapy:

Insertion of an indwelling pleural catheter for the management of malignant pleural effusion

Evidence for comparator:

Talc is the gold-standard pleurodesis agent used widely around the world. The dose and administration method for talc was matched to current UK standards.

Saline was chosen as a comparator as there is no evidence that this has the ability to induce pleurodesis.

Actual start date of recruitment	28 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 154
Worldwide total number of subjects	154
EEA total number of subjects	154

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)	56
From 65 to 84 years	90
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

18 sites from England and Scotland.
Recruitment took place from June 2012 to September 2016

Pre-assignment

Screening details:

Patients with malignant pleural effusion suitable for IPC insertion identified from routine practice.
Not eligible if pre-existing contraindication to pleurodesis (e.g. trapped lung) or if unable to comply with trial schedule

Period 1

Period 1 title	Day 10 randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Talc
Investigational medicinal product code	
Other name	Novatech Steritalc
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intrapleural use

Dosage and administration details:

4 grams made into slurry with 50mls normal saline

Arm title	Control

Arm description: -

Arm type	Placebo
Investigational medicinal product name	0.9% saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intrapleural use

Dosage and administration details:

50mls total

Number of subjects in period 1	Intervention	Control
Started	78	76
Completed	77	76
Not completed	1	0
Protocol deviation	1	-

Period 2	
Period 2 title	Follow-up over 10 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Intervention
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Talc
Investigational medicinal product code	
Other name	Novatech Steritalc
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intrapleural use
Dosage and administration details: 4 grams made into slurry with 50mls normal saline	
Investigational medicinal product name	0.9% saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intrapleural use
Dosage and administration details: 50mls total	
Arm title	Control
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	0.9% saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intrapleural use
Dosage and administration details: 50mls	

Number of subjects in period 2	Intervention	Control
Started	77	76
Completed	60	52
Not completed	17	24
Adverse event, serious fatal	7	14
Withdrawal from trial	10	10

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Reporting group values	Intervention	Control	Total
Number of subjects	78	76	154
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	67.7	68.7	
standard deviation	± 12.7	± 10.1	-
Gender categorical Units: Subjects			
Female	44	39	83
Male	34	37	71
ECOG performance status Units: Subjects			
PS0	8	10	18
PS1	38	33	71
PS2	23	16	39
PS3	8	16	24
Missing	1	1	2
Cancer types Units: Subjects			
Lung	20	25	45
Breast	15	16	31
Mesothelioma	13	10	23
Ovarian	6	5	11
Renal	5	4	9
Other	19	16	35
Lung entrapment of <25% at randomization Units: Subjects			
Yes	16	14	30

no	62	62	124

Number of pleural interventions in previous 3 months			
Units: Number			
median	1	1	
inter-quartile range (Q1-Q3)	1 to 2	0 to 2	-

End points

End points reporting groups	
Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: Pleurodesis success at 5 weeks	
End point title	Pleurodesis success at 5 weeks
End point description:	
End point type	Primary
End point timeframe:	
5 weeks post randomisation	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	70		
Units: Percentage				
Success	30	16		

Statistical analyses

Statistical analysis title	Primary outcome
Comparison groups	Intervention v Control
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	competing-risk time-to-event regression
Parameter estimate	Hazard ratio (HR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	3.92

Secondary: Pleurodesis success at 10 weeks

End point title	Pleurodesis success at 10 weeks

End point description:

End point type	Secondary

End point timeframe:

10 weeks post randomisation

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	70		
Units: percentage				
Success	35	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Pleurodesis success at 5 weeks (alternative)

End point title	Pleurodesis success at 5 weeks (alternative)

End point description:

End point type	Secondary

End point timeframe:

5 weeks

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	70		
Units: Percentage				
success	28	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Pleurodesis success at 10 weeks (alternative)

End point title	Pleurodesis success at 10 weeks (alternative)

End point description:

End point type	Secondary

End point timeframe:

10 weeks

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	69		
Units: Percentage				
success	30	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of fluid over 10 weeks

End point title	Volume of fluid over 10 weeks

End point description:

End point type	Secondary

End point timeframe:

Over 10 weeks

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: millilitre(s)				
median (inter-quartile range (Q1-Q3))	1350 (340 to 5680)	3640 (845 to 7605)		

Statistical analyses

No statistical analyses for this end point

Secondary: Additional procedures

End point title	Additional procedures

End point description:

End point type	Secondary

End point timeframe:

Over 10 weeks

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	73		
Units: Number				
Yes	5	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From consent to trial exit	
Assessment type	Systematic

Dictionary used	
Dictionary name	Locally determined
Dictionary version	n/a

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: All data regarding adverse events is available in the summary documents attached to this submission.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2012	Clarification of randomisation target of 154 patients • All references to SF-36 QoL questionnaire removed • Added exclusion criteria: patients must have access to phone for investigator trial contact • Clarified sample collection and analysis • Clarified procedure pre-randomisation • Clarified that patients may also be excluded from randomisation for clinical reasons other than x-ray appearances • Updated summary tables and clarified pre-randomisation day nomenclature • Stipulated a time window in which patients must have first IPC drainage post-randomisation • Clarified time window in which pts may have follow-up appointments • Clarified wording in safety reporting section and highlighted expected minor side effects from talc • Updated members of trial steering committee • New sites added: Preston, Portsmouth, Bristol Royal Infirmary
18 December 2012	New sites added: Worcester, North Staffordshire, North Tyneside, Middlesbrough, South Manchester and Blackpool • Creation of letter and short trial summary for district nurses • Alteration to primary endpoint, changing minimal fluid volume required for pleurodesis from 20mLs to 50mLs • Change to time limit given to patients to consider PIS • Removed requirement that trial CXR must be taken posterior-anterior (PA) specifically • Trial flow chart updated allowed patients to have follow up appointments at satellite centres • Allowance for patients to be approached as an inpatient but management must be as an outpatient for trial • Clarifications to adverse event and serious adverse event reporting procedures
01 August 2013	New sites added: London, Mansfield, Stockton-on-Tees and Sheffield • Clarification of wording of primary endpoint, removal of duplicate secondary endpoint and addition of new secondary endpoint 4.0 01/08/2013 47 • Clarification of definition of trapped lung in trial flow chart and protocol • Addition of new QoL questionnaire (QLQ-C30) for all new trial participants • Expanded the use of pleural manometry to all centres • Removed need for 0.9% saline placebo to be sources from particular manufacturer • Updated wording of how the primary outcome will be analysed • Updated membership of trial steering committee
01 January 2014	New sites added: Northampton, Ayr, Cambridge, and Aintree • Change of inclusion criteria to require WHO performance of 2 or better to be eligible. 3 if goes to 2 after drainage. • Allow pts with previous pleurodesis as long as more than 56 days before trial entry • Relax follow-up visits by allowing day 42 and 56 to be carried out over telephone • Allow carers/relatives to perform chest drains after day 28 post randomisation visit • Extend recruitment period to May 2015 • Relaxation of manometry recordings from every 100 ml to every 100-200 ml • Updated membership of TSC

09 September 2016	Remove interim analysis • add cough, chest pain/discomfort following drainage to expected AEs • amend reporting procedure for mild cough, chest pain/discomfort • extend trial end date to 31/10/2016 • update R&I contact details for SAE reporting

Notes:

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.

Only primary endpoint and major secondary endpoints are summarised here. For complete trial data and details of analyses, adverse events and all amendments, please refer to attachments.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29617585