Clinical trial results:
A Pragmatic Randomised Trial of Ibuprofen, Paracetamol, Steam and Delayed Prescribing for Patients with Respiratory Tract Infections in Primary Care

Summary

EudraCT number	2006-005740-83
Trial protocol	GB
Global end of trial date	03 December 2013

Results information

Result version number	v1 (current)
This version publication date	25 October 2020
First version publication date	25 October 2020

Trial information

Trial identification

Sponsor protocol code	4825

Additional study identifiers

ISRCTN number	ISRCTN38551726
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Southampton
Sponsor organisation address	Highfield, Southampton, United Kingdom, SO16 5ST
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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	03 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2013
Global end of trial reached?	Yes
Global end of trial date	03 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess, in a primary care setting, in patients with respiratory tract infection, whether:

1) there is a difference in the effectiveness between 3 different antipyretic regimes: ibuprofen treatment, paracetamol treatment and combined ibuprofen and paracetamol treatment
2) regular antipyretic dosing gives significantly better symptom and temperature control than 'as required' dosing
3) regular inhalation with steam further improves symptom control
4) there are any differences in antibiotic use and acceptability according to different methods of delaying antibiotic use

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2009
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: 889
Worldwide total number of subjects	889
EEA total number of subjects	889

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)	178
Adolescents (12-17 years)	68

Adults (18-64 years)	557
From 65 to 84 years	83
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study carried out a pragmatic randomised factorial trial in a primary care setting in patients with respiratory tract infection.
They examined the difference in the effectiveness of three different antipyretic regimens: ibuprofen, paracetamol, and combined ibuprofen and paracetamol.

Pre-assignment

Screening details:

Patients were excluded if they were asthmatic, had active or previous peptic ulceration, were hypersensitive to analgesics, and were unable to complete outcome measures.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

A statistician independent of the study team coordinated the randomisation using computer generated random numbers.

Arms

Are arms mutually exclusive?	Yes
Arm title	No prescription

Arm description:

No prescription of antibiotics

Arm type	Experimental
Investigational medicinal product name	No intervention
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Other use

Dosage and administration details:

No intervention

Arm title	Recontact

Arm description:

Recontacting the clinic to request a prescription by phone

Arm type	Experimental
Investigational medicinal product name	Ibuprofen, paracetamol, or both combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen, paracetamol, or both combined, four times a day for at least three days
Steam - advice to inhale with steam for at least 15 minutes (five minutes three times a day) or asked not to use steam

Arm title	Post date

Arm description:

post-dating the prescription

Arm type	Experimental
Investigational medicinal product name	Ibuprofen, paracetamol, or both combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen, paracetamol, or both combined, four times a day for at least three days
Steam - advice to inhale with steam for at least 15 minutes (five minutes three times a day) or asked not to use steam

Arm title	Collection

Arm description:

allowing patients to collect the prescription from the clinic themselves

Arm type	Experimental
Investigational medicinal product name	Ibuprofen, paracetamol, or both combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen, paracetamol, or both combined, four times a day for at least three days
Steam - advice to inhale with steam for at least 15 minutes (five minutes three times a day) or asked not to use steam

Arm title	Patient led

Arm description:

Giving prescriptions to patients and asking them to wait

Arm type	Experimental
Investigational medicinal product name	Ibuprofen, paracetamol, or both combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen, paracetamol, or both combined, four times a day for at least three days
Steam - advice to inhale with steam for at least 15 minutes (five minutes three times a day) or asked not to use steam

Arm title	Immediate antibiotics

Arm description:

Immediate antibiotics needed

Arm type	Experimental
Investigational medicinal product name	Ibuprofen, paracetamol, or both combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Immediate antibiotics
Ibuprofen, paracetamol, or both combined, four times a day for at least three days
Steam - advice to inhale with steam for at least 15 minutes (five minutes three times a day) or asked not to use steam

Number of subjects in period 1	No prescription	Recontact	Post date
Started	123	108	114
Completed	123	108	114

Number of subjects in period 1	Collection	Patient led	Immediate antibiotics
Started	105	106	333
Completed	105	106	333

Baseline characteristics

Reporting groups	
Reporting group title	No prescription
Reporting group description:	
No prescription of antibiotics	
Reporting group title	Recontact
Reporting group description:	
Recontacting the clinic to request a prescription by phone	
Reporting group title	Post date
Reporting group description:	
post-dating the prescription	
Reporting group title	Collection
Reporting group description:	
allowing patients to collect the prescription from the clinic themselves	
Reporting group title	Patient led
Reporting group description:	
Giving prescriptions to patients and asking them to wait	
Reporting group title	Immediate antibiotics
Reporting group description:	
Immediate antibiotics needed	

Reporting group values	No prescription	Recontact	Post date
Number of subjects	123	108	114
Age categorical Units: Subjects			
Age 3-90 years	123	108	114
Age continuous Units: years			
arithmetic mean	29	31	34
standard deviation	± 22	± 20	± 22
Gender categorical Units: Subjects			
Female	76	59	65
Male	46	48	45
unknown	1	1	4
Previous duration Units: days			
arithmetic mean	7.5	6.3	6.5
standard deviation	± 7.8	± 5.4	± 5.2
Mean severity of all symptoms at baseline Units: score			
arithmetic mean	0.94	0.92	0.98
standard deviation	± 0.44	± 0.42	± 0.44

Reporting group values	Collection	Patient led	Immediate antibiotics
Number of subjects	105	106	333

Age categorical Units: Subjects			
Age 3-90 years	105	106	333
Age continuous Units: years			
arithmetic mean	30	32	37
standard deviation	± 20	± 21	± 21
Gender categorical Units: Subjects			
Female	63	65	73
Male	41	40	258
unknown	1	1	2
Previous duration Units: days			
arithmetic mean	7.1	7.2	8.5
standard deviation	± 7.9	± 6.3	± 7.7
Mean severity of all symptoms at baseline Units: score			
arithmetic mean	0.99	0.94	1.15
standard deviation	± 0.42	± 0.42	± 0.45

Reporting group values	Total		
Number of subjects	889		
Age categorical Units: Subjects			
Age 3-90 years	889		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	401		
Male	478		
unknown	10		
Previous duration Units: days			
arithmetic mean			
standard deviation	-		
Mean severity of all symptoms at baseline Units: score			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	No prescription
Reporting group description:	
No prescription of antibiotics	
Reporting group title	Recontact
Reporting group description:	
Recontacting the clinic to request a prescription by phone	
Reporting group title	Post date
Reporting group description:	
post-dating the prescription	
Reporting group title	Collection
Reporting group description:	
allowing patients to collect the prescription from the clinic themselves	
Reporting group title	Patient led
Reporting group description:	
Giving prescriptions to patients and asking them to wait	
Reporting group title	Immediate antibiotics
Reporting group description:	
Immediate antibiotics needed	

Primary: Mean symptom severity, days 2-4

End point title	Mean symptom severity, days 2-4[1]
End point description:	
The primary outcome was symptom severity measured at the end of each day during days 2-4 of a two week symptom diary	
End point type	Primary
End point timeframe:	
days 2-4	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Immediate antibiotics not involved to the analyses

End point values	No prescription	Recontact	Post date	Collection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	108	114	105
Units: crude mean				
arithmetic mean (standard deviation)	1.62 (± 0.88)	1.60 (± 0.91)	1.82 (± 0.94)	1.68 (± 0.88)

End point values	Patient led			
Subject group type	Reporting group			
Number of subjects analysed	106			
Units: crude mean				
arithmetic mean (standard deviation)	1.75 (± 0.88)			

Statistical analyses

Statistical analysis title	Mean symptom severity, days 2-4
Comparison groups	No prescription v Recontact v Post date v Collection v Patient led
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	likelihood ratio test χ2

Primary: Symptoms rated as moderately bad

End point title	Symptoms rated as moderately bad[2]

End point description:

The diary was completed by patients until symptoms returned to normal. It used previously validated formats for rating symptoms (0=no problem, 6=as bad as it could be). Symptoms included feeling generally unwell, sleep disturbance, fever, interference with normal activities, sore throat, cough, short of breath, facial or sinus pain, earache, and runny or blocked nose.

End point type	Primary

End point timeframe:

2 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Immediate antibiotics not involved to the analyses

End point values	No prescription	Recontact	Post date	Collection
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	108	114	105
Units: score				
median (inter-quartile range (Q1-Q3))	3 (2 to 6.5)	4 (3 to 7)	4 (3 to 7)	4 (3 to 7)

End point values	Patient led			
Subject group type	Reporting group			
Number of subjects analysed	106			
Units: score				
median (inter-quartile range (Q1-Q3))	4 (3 to 7)			

Statistical analyses

Statistical analysis title	Symptoms rated as moderately bad
Comparison groups	No prescription v Recontact v Post date v Collection v Patient led
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	Likelihood ratio test χ2

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 1 month	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	No prescription
Reporting group description: No prescription of antibiotics	
Reporting group title	Recontact
Reporting group description: Recontacting the clinic to request a prescription by phone	
Reporting group title	Post date
Reporting group description: post-dating the prescription	
Reporting group title	Collection
Reporting group description: allowing patients to collect the prescription from the clinic themselves	
Reporting group title	Patient led
Reporting group description: Giving prescriptions to patients and asking them to wait	
Reporting group title	Immediate antibiotics
Reporting group description: Immediate antibiotics needed	

Serious adverse events	No prescription	Recontact	Post date
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 123 (0.00%)	0 / 108 (0.00%)	0 / 114 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Collection	Patient led	Immediate antibiotics
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 105 (0.00%)	0 / 106 (0.00%)	0 / 333 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	No prescription	Recontact	Post date
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 123 (32.52%)	17 / 108 (15.74%)	34 / 114 (29.82%)
Investigations			
Complications			
subjects affected / exposed	3 / 123 (2.44%)	4 / 108 (3.70%)	1 / 114 (0.88%)
occurrences (all)	3	4	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 123 (6.50%)	3 / 108 (2.78%)	9 / 114 (7.89%)
occurrences (all)	8	3	9
Vomiting			
subjects affected / exposed	9 / 123 (7.32%)	4 / 108 (3.70%)	8 / 114 (7.02%)
occurrences (all)	9	4	8
Abdominal pain			
subjects affected / exposed	15 / 123 (12.20%)	4 / 108 (3.70%)	11 / 114 (9.65%)
occurrences (all)	15	4	11
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 123 (4.07%)	2 / 108 (1.85%)	5 / 114 (4.39%)
occurrences (all)	5	2	5

Non-serious adverse events	Collection	Patient led	Immediate antibiotics
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 105 (22.86%)	35 / 106 (33.02%)	131 / 333 (39.34%)
Investigations			
Complications			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	8 / 333 (2.40%)
occurrences (all)	1	0	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 105 (6.67%)	10 / 106 (9.43%)	28 / 333 (8.41%)
occurrences (all)	7	10	28
Vomiting			

subjects affected / exposed	2 / 105 (1.90%)	9 / 106 (8.49%)	25 / 333 (7.51%)
occurrences (all)	2	9	25
Abdominal pain			
subjects affected / exposed	13 / 105 (12.38%)	15 / 106 (14.15%)	62 / 333 (18.62%)
occurrences (all)	13	15	62
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 105 (0.95%)	4 / 106 (3.77%)	8 / 333 (2.40%)
occurrences (all)	1	4	8

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24162940

http://www.ncbi.nlm.nih.gov/pubmed/24603565