Clinical trial results:
An open label pragmatic randomised controlled trial of nicotine patch preloading for smoking cessation.

Summary

EudraCT number	2011-005134-19
Trial protocol	GB
Global end of trial date	12 May 2016

Results information

Result version number	v1 (current)
This version publication date	28 April 2017
First version publication date	28 April 2017

Trial information

Trial identification

Sponsor protocol code	RG_11-171

Additional study identifiers

ISRCTN number	ISRCTN33031001
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Heather House, University of Oxford, 0044 01865 572245, heather.house@admin.ox.ac.uk
Scientific contact	Heather House, University of Oxford, 0044 01865 572245, heather.house@admin.ox.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	01 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2016
Global end of trial reached?	Yes
Global end of trial date	12 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives are:

1. To examine the relative efficacy of nicotine patch worn for four weeks prior to quitting plus standard NHS care post-quit versus standard care only in smokers undergoing NHS treatment for tobacco dependence.
2. To examine the adverse effects and safety of the nicotine pre-treatment.

Protection of trial subjects:

A risk assessment was carried out in accordance with MHRA guidance on Risk Adapted Approaches to Monitoring. A suitable monitoring plan was drawn up and appropriate on-site and central monitoring performed.

Background therapy:

In both arms, at the first and second contacts in both arms, we facilitated contact between the participant and the local stop smoking services and wrote a referral letter to encourage the stop smoking service to work with us on respecting the preloading treatment. In particular, we asked the stop smoking advisors to ignore the presence or absence of preloading when discussing and recommending pharmacotherapy for use to support the quit attempt. We especially asked advisors to feel free to use varenicline, which starts prior to quit day and hence would be used concurrently with nicotine preloading. This is because we were keen that the treatment provided by the stop smoking services did not differ between trial arms.

The NHS trains stop smoking advisors to give weekly behavioural support starting 1-2 weeks prior to quit day and continuing until at least four weeks after quit day. This support addresses issues such as planning for the quit day, the 'not a puff rule', and how to deal with difficult situations, such as others smoking around the quitter. It also provides monitoring of behaviour and validation of abstinence through carbon monoxide testing. The support is largely withdrawal-orientated therapy.

Evidence for comparator:

The research team were keen to offer participants in the control arm a placebo, but the funding would not allow this. We were concerned that offering no treatment would lead to disengagement and, to counteract this, we developed a behavioural intervention which could seem plausible to participants but had no evidence that it would increase abstinence. We asked participants to consider their smoking pattern, the triggers for particular cigarettes, and to plan ways to reduce these cues. Such a process is standard in smoking cessation support anyway, so that participants in the intervention group were likely to engage in this after preloading and in preparation for quitting. As in the intervention group, the control group received a booklet outlining this process, which was designed to be comparable to the booklet supplied to the intervention group. As in the intervention group, participants in the control group were referred to the NHS Stop Smoking Service to commence a quit attempt between three and five weeks after enrolment.

Actual start date of recruitment	13 August 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: 1792
Worldwide total number of subjects	1792
EEA total number of subjects	1792

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)	1561
From 65 to 84 years	229
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

four recruitment centres Birmingham, Bristol and Nottingham, all recruiting between 1 February 2012 and March 2016

Pre-assignment

Screening details:

Inclusion criteria:
Regular smokers of cigarettes, cigars, and rollup tobacco cigarettes, with or without marijuana aged ≥18 years of age.
People who would be suitable for preloading in the judgement of the researcher
Prepared to set a quit day in four weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	preloading

Arm description:

In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.

Arm type	Experimental
Investigational medicinal product name	Nicotine replacement therapy patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

21 mg Niquitin CQ Glaxo Smith Kline Consumer Healthcare daily nicotine patch worn for four weeks before their smoking quit day, from the day of their enrolment. They were advised to wear the patch for 24 hours a day.

Arm title	control

Arm description:

standard smoking cessation support only

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	preloading	control
Started	899	893
6 months	728	733
Completed	689	700
Not completed	210	193
Adverse event, serious fatal	-	2

died	4	-
Lost to follow-up	195	171
withdrawn	11	20

Baseline characteristics

Reporting groups	
Reporting group title	preloading
Reporting group description:	
In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.	
Reporting group title	control
Reporting group description:	
standard smoking cessation support only	

Reporting group values	preloading	control	Total
Number of subjects	899	893	1792
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			
age continuous			
Units: years			
arithmetic mean	49.1	48.8	
standard deviation	± 13.3	± 13.4	-
Gender categorical			
Units: Subjects			
Female	426	423	849
Male	473	470	943
carbon monoxide			
carbon monoxide reading			
Units: parts per million			
arithmetic mean	23.5	23.8	
standard deviation	± 12.3	± 12.8	-
nicotine dependence			
nicotine dependence (NCSCT)			
Units: scale 0 to 10			
arithmetic mean	5.22	5.2	
standard deviation	± 2.2	± 2.24	-

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all patients randomised irrespective of whether the participants received any trial medication and irrespective of whether they completed

Reporting group values	ITT		
Number of subjects	1792		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
age continuous			
Units: years arithmetic mean standard deviation	 48.9 ± 13.4		
Gender categorical Units: Subjects			
Female Male	849 943		
carbon monoxide			
carbon monoxide reading			
Units: parts per million arithmetic mean standard deviation	 23.7 ± 12.5		
nicotine dependence			
nicotine dependence (NCSCT)			
Units: scale 0 to 10 arithmetic mean standard deviation	 5.21 ± 2.2		

End points

End points reporting groups

Reporting group title	preloading
Reporting group description:	
In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.	
Reporting group title	control
Reporting group description:	
standard smoking cessation support only	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all patients randomised irrespective of whether the participants received any trial medication and irrespective of whether they completed	

Primary: smoking abstinence at 6 months (russell criteria)

End point title	smoking abstinence at 6 months (russell criteria)
End point description:	
smoking abstinence 6 months after quit date	
End point type	Primary
End point timeframe:	
6 months after quit date	

End point values	preloading	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899[1]	893[2]		
Units: 0 1				
no	573	608		
yes	326	285		

Notes:

[1] - ITT

[2] - ITT

Statistical analyses

Statistical analysis title	abstinence at 6 months
Statistical analysis description:	
logistic regression with adjustment for centre	
Comparison groups	preloading v control
Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.62

Secondary: russell standard abstinence at 4 weeks

End point title	russell standard abstinence at 4 weeks
End point description: validated abstinence at 4 weeks after quit date	
End point type	Secondary
End point timeframe: 4 weeks after quit date	

End point values	preloading	control	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	899	893	1792	
Units: 0 1				
no	573	608	1181	
yes	326	285	611	

Statistical analyses

Statistical analysis title	validated abstinence at 4 weeks
Statistical analysis description: logistic regression for validated abstinence at 4 weeks adjusted for centre	
Comparison groups	preloading v control
Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.48

Secondary: 7 day point prevalence abstinence at 4 weeks

End point title	7 day point prevalence abstinence at 4 weeks
End point description: point prevalence abstinence at 4 weeks after quit date	
End point type	Secondary
End point timeframe: 4 weeks after quit date	

End point values	preloading	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	893		
Units: 0 1				
no	580	605		
yes	319	288		

Statistical analyses

Statistical analysis title	7 day point prevalence abstinence at 4 weeks
Statistical analysis description: logistic regression adjusted for centre	
Comparison groups	preloading v control
Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.41

Secondary: 7 day point prevalence abstinence at 6 months

End point title	7 day point prevalence abstinence at 6 months
End point description: 7 day point prevalence abstinence at 6 months after quit date	
End point type	Secondary
End point timeframe: 6 months after quit date	

End point values	preloading	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	893		
Units: 0 1				
no	699	712		
yes	200	181		

Statistical analyses

Statistical analysis title	7 day point prevalence abstinence at 6 months
Statistical analysis description: logistic regression adjusted for centre	
Comparison groups	preloading v control
Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.41

Secondary: 12 months validated abstinence

End point title	12 months validated abstinence
End point description: 12 months validated abstinence after quit date	
End point type	Secondary
End point timeframe: 12 months after quit date	

End point values	preloading	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	893		
Units: 0 1				
no	773	792		
yes	126	101		

Statistical analyses

Statistical analysis title	12 months validated abstinence
Statistical analysis description: logistic regression adjusted for centre	
Comparison groups	preloading v control
Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.69

Secondary: 7 day point prevalence abstinence at 12 months

End point title	7 day point prevalence abstinence at 12 months
End point description: 7 day point prevalence abstinence 12 months after quit date	
End point type	Secondary
End point timeframe: 12 months after quit date	

End point values	preloading	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	893		
Units: 0 1				
no	698	723		
yes	201	170		

Statistical analyses

Statistical analysis title	7 day point prevalence abstinence at 12 months
Statistical analysis description: logistic regression with adjustment for centre	
Comparison groups	preloading v control

Number of subjects included in analysis	1792
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.54

Adverse events

Adverse events information

Timeframe for reporting adverse events:

adverse events are those that occurred after baseline and until one week after quit day. In the protocol, we deemed that we would report only adverse events of moderate severity or above i.e. those that hindered normal activities

Adverse event reporting additional description:

we elicited adverse events from participants in both arms at contacts -3 weeks (one week after baseline) and at +1 week (five weeks after baseline and one week after quit day).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	preloading

Reporting group description:

In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.

Reporting group title	control

Reporting group description:

standard smoking cessation support only

Serious adverse events	preloading	control	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 899 (0.89%)	8 / 893 (0.90%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Investigations			
Aspiration pleural cavity			
subjects affected / exposed	1 / 899 (0.11%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 899 (0.00%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	2 / 899 (0.22%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 899 (0.00%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 899 (0.11%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Oesophageal carcinoma			
subjects affected / exposed	0 / 899 (0.00%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pneumonia			
subjects affected / exposed	0 / 899 (0.00%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	1 / 899 (0.11%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 899 (0.00%)	2 / 893 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			

Psychotic disorder			
subjects affected / exposed	1 / 899 (0.11%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intentional self-injury			
subjects affected / exposed	1 / 899 (0.11%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 899 (0.00%)	1 / 893 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pelvic fracture			
subjects affected / exposed	1 / 899 (0.11%)	0 / 893 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	preloading	control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 899 (15.46%)	85 / 893 (9.52%)	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	4 / 899 (0.44%)	8 / 893 (0.90%)	
occurrences (all)	4	8	
Nervous system disorders			
Abnormal dreams			
subjects affected / exposed	9 / 899 (1.00%)	1 / 893 (0.11%)	
occurrences (all)	9	1	
Dizziness			
subjects affected / exposed	15 / 899 (1.67%)	6 / 893 (0.67%)	
occurrences (all)	15	6	

Headache			
subjects affected / exposed	14 / 899 (1.56%)	3 / 893 (0.34%)	
occurrences (all)	14	3	
Poor quality sleep			
subjects affected / exposed	20 / 899 (2.22%)	3 / 893 (0.34%)	
occurrences (all)	20	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 899 (1.11%)	5 / 893 (0.56%)	
occurrences (all)	10	5	
Fatigue			
subjects affected / exposed	6 / 899 (0.67%)	0 / 893 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 899 (0.67%)	3 / 893 (0.34%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	8 / 899 (0.89%)	3 / 893 (0.34%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	30 / 899 (3.34%)	8 / 893 (0.90%)	
occurrences (all)	30	8	
Vomiting			
subjects affected / exposed	14 / 899 (1.56%)	3 / 893 (0.34%)	
occurrences (all)	14	3	
Respiratory, thoracic and mediastinal disorders			
Infection			
subjects affected / exposed	1 / 899 (0.11%)	4 / 893 (0.45%)	
occurrences (all)	1	4	
Influenza like illness			
subjects affected / exposed	7 / 899 (0.78%)	3 / 893 (0.34%)	
occurrences (all)	7	3	
Nasopharyngitis			
subjects affected / exposed	4 / 899 (0.44%)	7 / 893 (0.78%)	
occurrences (all)	4	7	

Skin and subcutaneous tissue disorders Skin irritation subjects affected / exposed occurrences (all)	 5 / 899 (0.56%) 5	 2 / 893 (0.22%) 2	
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	 5 / 899 (0.56%) 5	 4 / 893 (0.45%) 4	
Musculoskeletal and connective tissue disorders Musculoskeletal disorder subjects affected / exposed occurrences (all)	 10 / 899 (1.11%) 10	 7 / 893 (0.78%) 7	

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