Clinical trial results:
An open randomised trial of patient controlled analgesia (PCA) versus routine care in patients with non-traumatic abdominal pain attending the Emergency Department. There is also a parallel, open randomised trial of patient controlled analgesia (PCA) versus routine care in patients with pain from traumatic injuries attending the Emergency Department which has been reported on elsewhere.

Summary

EudraCT number	2011-000194-31
Trial protocol	GB
Global end of trial date	30 June 2014

Results information

Result version number	v1 (current)
This version publication date	16 November 2019
First version publication date	16 November 2019

Trial information

Trial identification

Sponsor protocol code	PenCTU/2010/CTIMP-004

Additional study identifiers

ISRCTN number	ISRCTN25343280
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	R&D Number: 11/P/055, IRAS Number: 74960, REC Reference: 11/SC/0151, PenCTU Study Number: PenCTU/2010/CTIMP-004

Notes:

Sponsors

Sponsor organisation name	University Hospitals Plymouth NHS Trust (formerly Plymouth Hospitals NHS Trust)
Sponsor organisation address	Research Office, L2 MSCP, Bircham Park Offices, 1 Roscoff Rise, Derriford, Plymouth, United Kingdom, PL6 5FP
Public contact	Chris Hayward, Quality Assurance Manager, University of Plymouth, Peninsula Clinical Trials Unit (PenCTU), 01752 431020, christopher.hayward@pms.ac.uk
Scientific contact	Prof Jason Smith, Consultant in Emergency Medicine, University Hospitals Plymouth NHS Trust, Emergency Department, 01752 437629, jasonesmith@nhs.net

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The research actually comprised two randomised controlled trials run in parallel, with two distinct patient populations, two different sample size calculations and the data were analysed independently in the two trials. The main objective was to compare patient controlled analgesia to nurse titrated analgesia (routine care) in adult emergency patients who present to the Emergency Department (ED) in moderate or severe pain from traumatic injury or with moderate or severe non-traumatic abdominal pain requiring IV analgesia and hospital admission. This EudraCT record has been populated with data from patients with non-traumatic abdominal pain. However, a publication link (https://www.ncbi.nlm.nih.gov/pubmed/26094763) is included under 'Online references' for the group with pain from traumatic injury.

Protection of trial subjects:

The study is approved by the MHRA and the South Central - Southampton A Research Ethics Committee (NRES). Study monitoring is conducted by the Peninsula Clinical Trials Unit (PenCTU) and a Trial Steering Committee (TSC) and an Independent Data Monitoring Committee (IDMC) are set up for the study oversight.

Background therapy:

Pain relief (morphine) administered by PCA.

Evidence for comparator:

Pain relief (morphine) administered as per routine care (TAU).

Actual start date of recruitment	05 July 2011
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: 209
Worldwide total number of subjects	209
EEA total number of subjects	209

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)	188
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

200 adult patients arriving at ED presenting with moderate or severe pain from non-traumatic abdominal pain will be targeted for recruitment. Expected duration of subject participation is 12 hours starting from the time that baseline VAS score is recorded, immediately after obtaining written informed consent

Pre-assignment

Screening details:

Patients between 18 and 75 years of age inclusive, Non-traumatic abdominal pain, Patients with moderate or severe pain who would routinely be prescribed IV morphine as part of standard care, Patients who are likely to remain in hospital for at least 12 hours from the time of enrolment, Provision of informed consent.

Pre-assignment period milestones

Number of subjects started	209
Number of subjects completed	209

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment as Usual (TAU)

Arm description:

Participants in the control group will continue to receive routine care as per local policy/protocol. In the ED, this comprises repeated doses of nurse-delivered IV morphine, as necessary to achieve adequate analgesia (VAS ≤44mm). Once admitted to an inpatient ward, routine care in accordance with local policy/protocol comprises further administration of opioid analgesia in the form of oral morphine solution, or subcutaneous morphine if nil by mouth, as required.

Arm type	Active comparator
Investigational medicinal product name	Morphine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Intravenous use, Oral use, Subcutaneous use

Dosage and administration details:

In the ED: Continued morphine sulphate IV solution 1mg/ml: delivered and titrated by nurse as necessary to achieve adequate analgesia (VAS ≤ 44mm), as per local policy/protocol. Once admitted to ward: Morphine sulphate 2mg/ml oral solution, 20-30mg, 2 hourly PRN, as per local policy/protocol Or, if patient is nil-by mouth: Morphine sulphate 10mg/ml subcutaneous injection, 5-12.5mg, 2 hourly, as per local policy/protocol.

Arm title	Patient Controlled Analgesia (PCA)

Arm description:

Participants in the a PCA group will receive a PCA device, via which they can administer further IV morphine boluses. The PCA device will remain in place for a minimum period of twelve hours, from the time of informed consent and collection of baseline VAS score provision.

Arm type	Experimental

Investigational medicinal product name	Morphine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Morphine sulphate IV solution 1mg/ml: delivered via PCA device - 1mg bolus dose with 5 minute lock out for a minimum period of 12 hours (in the ED and on inpatient ward).

Number of subjects in period 1	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)
Started	105	104
Completed	97	99
Not completed	8	5
VAS booklet lost	3	3
Insufficient VAS data	3	-
Local difficulties in implementing the protocol	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment as Usual (TAU)
Reporting group description:	
Participants in the control group will continue to receive routine care as per local policy/protocol. In the ED, this comprises repeated doses of nurse-delivered IV morphine, as necessary to achieve adequate analgesia (VAS ≤44mm). Once admitted to an inpatient ward, routine care in accordance with local policy/protocol comprises further administration of opioid analgesia in the form of oral morphine solution, or subcutaneous morphine if nil by mouth, as required.	
Reporting group title	Patient Controlled Analgesia (PCA)
Reporting group description:	
Participants in the a PCA group will receive a PCA device, via which they can administer further IV morphine boluses. The PCA device will remain in place for a minimum period of twelve hours, from the time of informed consent and collection of baseline VAS score provision.	

Reporting group values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)	Total
Number of subjects	105	104	209
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	94	94	188
From 65-84 years	11	10	21
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	69	70	139
Male	36	34	70
Time of Recruitment Units: Subjects			
Morning (0600-1159)	35	38	73
Afternoon (1200-2200)	62	61	123
Excluded from Analysis	8	5	13
Recruitment Centre Units: Subjects			
Centre 1	61	66	127
Centre 2	16	15	31
Centre 3	11	11	22
Centre 4	9	7	16
Excluded from Analysis	8	5	13
Clinical Diagnosis Units: Subjects			
Bowel Pathology	14	16	30
Gall Bladder Pathology	15	13	28

Renal or Ureteric Pathology	8	4	12
Pancreatic Pathology	8	9	17
Appendix Pathology	7	6	13
Renal or Ureteric Pathology (Stone Passed)	14	14	28
Gynae Pathology (inc. Ovarian)	7	4	11
Oesophagitis or Gastritis	4	4	8
Abdominal Pain	14	20	34
Other (inc. Post-op Pain, Hepatic Neoplasm)	6	9	15
Excluded from Analysis	8	5	13
Pre-Admission Analgesia			
At least one dose in 24 hours before ED arrival.			
Units: Subjects			
Analgesic Gas	3	7	10
Non-Steroidal Anti-Inflammatory Drug	15	9	24
Paracetamol	33	32	65
Weak Opioid	14	9	23
Excluded from Analysis	8	5	13
No Pre-Admission Analgesia (in 24hrs of arrival)	32	42	74
Verbal Pain Score			
0-10 as recorded on hospital administration system			
Units: Score (0-10)			
median	8	8	
inter-quartile range (Q1-Q3)	6 to 9	6 to 9	-
Visual Analogue Pain Score			
At time of consent, cm			
Units: Centimeter			
median	6.1	4.8	
inter-quartile range (Q1-Q3)	3.2 to 7.7	2.2 to 6.8	-
Time from Arrival in ED to Randomisation			
Units: Minutes			
arithmetic mean	162.4	164.7	
standard deviation	± 83.9	± 83.4	-
Preadmission Analgesia: Participants with Pre-Admission Morphine			
Units: Subjects			
arithmetic mean	9.1	8.9	
standard deviation	± 6.1	± 3.0	-
Preadmission Analgesia: All Participants			
Units: Subjects			
arithmetic mean	3.3	3.0	
standard deviation	± 5.7	± 4.8	-

End points

End points reporting groups

Reporting group title	Treatment as Usual (TAU)

Reporting group description:

Participants in the control group will continue to receive routine care as per local policy/protocol. In the ED, this comprises repeated doses of nurse-delivered IV morphine, as necessary to achieve adequate analgesia (VAS ≤44mm). Once admitted to an inpatient ward, routine care in accordance with local policy/protocol comprises further administration of opioid analgesia in the form of oral morphine solution, or subcutaneous morphine if nil by mouth, as required.

Reporting group title	Patient Controlled Analgesia (PCA)

Reporting group description:

Participants in the a PCA group will receive a PCA device, via which they can administer further IV morphine boluses. The PCA device will remain in place for a minimum period of twelve hours, from the time of informed consent and collection of baseline VAS score provision.

Primary: Total pain experienced: Primary and Sensitivity Analyses

End point title	Total pain experienced: Primary and Sensitivity Analyses

End point description:

The primary outcome measure is the visual analogue pain rating scale (VAS) as a unidimensional measure of pain. The primary endpoint will be the difference between the intervention (PCA) and control (TAU) groups with regard to overall pain experience over the 12 hour period, captured by using a standardised area under the curve (max score 100) of the participant-recorded hourly serial VAS pain measurements. Sensitivity 1 = Pain scored as zero for periods of sleep. Sensitivity 2 = Missing pain scores from theatre withdrawals imputed using linear interpolation from last recorded pain score to zero at 12 hr time point. Sensitivity 3 = Includes data from site who had local difficulties in implementing the protocol. Sensitivity 4 = Excludes data from 35 participants with >5 minutes between time of first pain score and time of randomisation.

End point type	Primary

End point timeframe:

On obtaining informed consent, the participant will mark their VAS pain score. Participants are then prompted to record their VAS pain score at hourly intervals by a bleep from the electronic timer.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Pain score				
arithmetic mean (standard deviation)				
Primary Analysis	47.3 (± 24.7)	35.3 (± 25.8)		
Sensitivity 1	37.7 (± 21.5)	28.2 (± 22.3)		
Sensitivity 2	46.7 (± 24.7)	34.7 (± 25.5)		
Sensitivity 3	47.7 (± 24.6)	35.2 (± 25.6)		
Sensitivity 4	49.2 (± 23.3)	36.7 (± 25.7)		

Statistical analyses

Statistical analysis title	Adjusted Analysis

Statistical analysis description:

Adjusted for stratification variables (time of first pain score and recruitment centre) and baseline pain score.

Comparison groups	Treatment as Usual (TAU) v Patient Controlled Analgesia (PCA)
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	11.9

Notes:

[1] - Primary analyses undertaken on an 'intention-to-treat' (ITT) basis.

Secondary: Total morphine

End point title	Total morphine

End point description:

None.

End point type	Secondary

End point timeframe:

Sum of pre-admission morphine, morphine from time of admission to time of recruitment, and morphine delivered during 12 hour study period.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: milligram(s)				
arithmetic mean (standard deviation)	23.6 (± 13.1)	36.1 (± 22.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total morphine during 12 hour study period

End point title	Total morphine during 12 hour study period

End point description:

None.

End point type	Secondary

End point timeframe:

Dose information will be recorded on hospital drug charts by staff responsible for clinical management of the patient as per routine practice. PCA usage will be obtained from the PCA devices which log dosage every hour.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: milligram(s)				
arithmetic mean (standard deviation)	10.7 (± 9.6)	23.6 (± 20.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of study period with pain VAS >4.4cm

End point title	Percentage of study period with pain VAS >4.4cm

End point description:

None.

End point type	Secondary

End point timeframe:

VAS score collected at hourly intervals during the 12 hour study period.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: millimeter(s)				
arithmetic mean (standard deviation)	46.9 (± 30.5)	32.6 (± 32.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of study period asleep

End point title	Percentage of study period asleep

End point description:

VAS sheet will have a tickbox used by the participant to indicate periods of sleep. When a participant hears a bleep reminder after waking from a period of sleep, s/he will complete the appropriate VAS

score as usual (i.e. on the sheet corresponding to the display on the timer) and will then indicate their prior period of sleep by ticking the tickbox on the previous relevant sheet(s).

End point type	Secondary

End point timeframe:

Participants will retrospectively record periods of sleep on the VAS pain score sheet.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: hour				
arithmetic mean (standard deviation)	18.6 (± 19.2)	19.7 (± 18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

None.

End point type	Secondary

End point timeframe:

Following the participant's discharge, the length of stay in hospital will be obtained from the Patient Administration System (PAS) (or equivalent) by the RN and recorded in the CRF.

End point values	Treatment as Usual (TAU)	Patient Controlled Analgesia (PCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: day				
arithmetic mean (standard deviation)	3.6 (± 3.0)	3.3 (± 3.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs reported to Sponsor and PenCTU within 24hrs. Sponsor will report fatal/ life-threatening SUSARS to the MHRA and REC within 7 days.

Adverse event reporting additional description:

SUSARs which are not fatal or life-threatening are reported by the sponsor to the MHRA and REC within 15 days after the sponsor first becomes aware of the reaction.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Both Arms - TAU and PCA

Reporting group description: -

Serious adverse events	Both Arms - TAU and PCA		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 209 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Both Arms - TAU and PCA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 209 (2.39%)		
Skin and subcutaneous tissue disorders			
Urticaria	Additional description: Urticaria at canulation site		
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 209 (1.91%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2011	Protocol V2.0, 16 Nov 2011: the protocol has been amended for two primary reasons: 1) to slightly alter the trial entry criteria to enhance recruitment and to clarify existing criteria 2) to introduce an additional, non interventional, questionnaire based follow up study investigating frequency of chronic pain development six months after participation in the main, interventional phase of the trial. The opportunity has been taken also to update contact details following changes to email addresses
23 April 2012	Protocol V3.0, 23 Apr 2012: References to Derriford Hospital as the sole Investigator Site have been modified / removed to reflect REC approval of additional sites. An additional VAS score collected after the 12 hour study period also added.
26 June 2012	Protocol V4.0, 26 Jun 2012: Remove the question relating to morphine-related adverse events from the additional follow-up questionnaire.

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.

See publication for strengths and limitations of the study - https://www.ncbi.nlm.nih.gov/pubmed/26094712

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26094763

http://www.ncbi.nlm.nih.gov/pubmed/26094712