# Clinical trial results:
# The use of Ketamine as an anaesthetic during electroconvulsive therapy (ECT) for depression: does it improve treatment outcome?

## Summary

| | |
|---|---|
| EudraCT number | 2011-000396-14 |
| Trial protocol | GB |
| Global end of trial date | 18 February 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 July 2018 |
| First version publication date | 29 July 2018 |
| Summary attachment (see zip file) | Ketamine as the anaesthetic for electroconvulsive therapy: The KANECT randomised controlled trial (Fernie et al (2017) Ketamine as the anaesthetic.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 3/006/11 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01306760 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Aberdeen/NHS-Grampian |
| Sponsor organisation address | Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB |
| Public contact | Research Governance Office, University of Aberdeen/NHS-Grampian, 44 (0) 1224 551123, researchgovernance@abdn.ac.uk |
| Scientific contact | Research Governance Office, University of Aberdeen/NHS-Grampian, 44 (0) 1224 551123, researchgovernance@abdn.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 | 22 September 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 February 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main research question is whether the use of ketamine as the anaesthetic for ECT treatment for depression improves the treatment outcome with respect to speed of response and reduction in side effects when compared to conventional anaesthesia.

Protection of trial subjects:

An unblinding procedure was specified should the medical need arise.
An independent Trial Steering Committee was in place and met approximately every 6 months while recruitment was open.

Background therapy:

We placed no restrictions on concomitant medication prescribing during the course of the trial except that benzodiazepines were withdrawn prior to ECT. No restrictions were placed on any rescue medications.

Evidence for comparator:

The active comparator, propofol, was used in 88.2% of ECT treatments in Scotland at the time the trial took place.

Reference: Scottish ECT Accreditation Network. Scottish ECT Accreditation Network Annual Report 2015: A summary of ECT in Scotland for 2014. Edinburgh, Scotland: ISD Scotland Publications; 2015.

| | |
|---|---|
| Actual start date of recruitment | 01 November 2011 |
| 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: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

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) | 35 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were receiving ECT for major depression on an informal basis at the Royal Cornhill Hospital, Aberdeen, Scotland between
November 2011 and December 2013. The final assessment of the final patient was completed in February 2014. The ethnicity of
all patients was White British. All participants provided informed consent.

### Pre-assignment

Screening details:

Eligible if receiving ECT on an informal basis (i.e. not detained), considered fit by an anaesthetist (American Society of Anaesthesiologists physical status classification system score of 1 or 2), had no comorbid psychiatric diagnoses recorded by the treating psychiatrist & were between the ages of 18 75. Exclusion criteria applied.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

Randomisation recorded in medical notes as Drug A or B by the Principal Investigator or ECT nurses. Patients were first assessed before randomisation. All post-ECT assessments were conducted by researchers blinded to the anaesthetic assignment.
All analyses were conducted by a researcher blind to the group assignment.
The decision on management of the ECT course was taken by the patients' treating clinicians, who were blind to anaesthetic assignment.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ketamine |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ketamine |
| Investigational medicinal product code | |
| Other name | Ketalar |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

An intravenous cannula was inserted in the non-isolated arm. The patients in the ketamine group were administered a hypnotic dose of ketamine of up to 2 mg/kg followed by limb isolation and subsequent administration of the muscle relaxant suxamethonium (0.5-1 mg/kg).

| | |
|---|---|
| **Arm title** | Propofol |

Arm description: -

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Propofol |
| Investigational medicinal product code | |
| Other name | Diprivan 1% |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

A hypnotic dose of propofol up to 2.5 mg/kg followed by limb isolation and administration of

suxamethonium (0.5-1 mg/kg).

Heart rate, 3 lead ECG, Oxygen Saturation (SpO2), fractional inspired oxygen (FiO2), and end-tidal CO2 (EtC02) were monitored continuously during the procedure. All participants received positive pressure ventilation with 100% oxygen during the procedure until spontaneous respiration resumed. Non-invasive blood pressure was measured before the administration of the anaesthetic, immediately post seizure and repeated if necessary. In the recovery room patients received oxygen-enriched air via a facemask, while non-invasive blood pressure and SpO2 were monitored.

| **Number of subjects in period 1** | Ketamine | Propofol |
|---|---|---|
| Started | 20 | 20 |
| Completed post-ECT4 assessments | 14 | 17 |
| Completed post-ECT assessment | 16 | 17 |
| Completed 1-month post-ECT assessments | 13 | 13 |
| Completed | 13 | 13 |
| Not completed | 7 | 7 |
| Consent withdrawn by subject | 1 | - |
| Physician decision | 3 | 1 |
| Maintenance ECT within follow-up period | 1 | 1 |
| withdrawn due to exposure to legal high | - | 1 |
| Lost to follow-up | 2 | 3 |
| Prescibed another course of ECT within follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ketamine |
| Reporting group description: - | |
| Reporting group title | Propofol |
| Reporting group description: - | |

| Reporting group values | Ketamine | Propofol | Total |
|---|---|---|---|
| Number of subjects | 20 | 20 | 40 |
| Age categorical<br>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) | 18 | 17 | 35 |
| From 65-84 years | 2 | 3 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 51.76 | 49.88 | |
| standard deviation | ± 9.97 | ± 12.53 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 11 | 11 | 22 |
| Male | 9 | 9 | 18 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ketamine |
| Reporting group description: - | |
| Reporting group title | Propofol |
| Reporting group description: - | |

### Primary: Number of ECT treatments

| | |
|---|---|
| End point title | Number of ECT treatments |

End point description:

The decision to end the ECT course was taken by the participant's treating clinician who was blind to anaesthetic assignment.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Number of ECT treatments in the ECT course. Includes 2 of 16 participants in the ketamine group and 2 of 19 in the propofol group who received 4 ECTs or less. Please refer to Table on page 5 or CONSORT flow diagram in results paper for more info.

| End point values | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[1] | 19[2] | | |
| Units: ECT treatments | | | | |
| arithmetic mean (standard deviation) | 7.88 (± 3.18) | 7.26 (± 2.23) | | |

Notes:

[1] - Completed post-ECT assessment

[2] - Completed post-ECT assessment

### Statistical analyses

| Statistical analysis title | t-test |
|---|---|

Statistical analysis description:

The number of ECT treatments received by patients in each group was compared using an independent samples t-test.

| | |
|---|---|
| Comparison groups | Ketamine v Propofol |
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | > 0.05 [3] |
| Method | t-test, 2-sided |

Notes:

[3] - $t(33) < 1.0$, $p > .05$, $d = 0.23$.

### Primary: Hamilton Depression Rating Scale (HDRS) - Acute analysis

| | |
|---|---|
| End point title | Hamilton Depression Rating Scale (HDRS) - Acute analysis |

End point description:

An acute effects analysis, Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared ($\eta p^2$) provided an estimate of effect size with 95% confidence intervals (95% CI)

| End point type | Primary |
|---|---|

End point timeframe:

compared outcomes pre-ECT with post-ECT4.
Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134
Consult Table on page 5 for number of subjects in analyses

| **End point values** | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[4] | 19[5] | | |
| Units: HDRS score | | | | |
| arithmetic mean (standard deviation) | 17.25 (± 6.88) | 13.58 (± 5.71) | | |

Notes:

[4] - Completed post-ECT 4 assessment

[5] - Completed post-ECT 4 assessment

### Statistical analyses

| **Statistical analysis title** | ANCOVA - acute HDRS |
|---|---|

Statistical analysis description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

| Comparison groups | Ketamine v Propofol |
|---|---|
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [6] |
| Method | ANCOVA |

Notes:

[6] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

### Primary: Montgomery-Asberg Depression Rating Scale (MADRS) - Acute analysis

| End point title | Montgomery-Asberg Depression Rating Scale (MADRS) - Acute analysis |
|---|---|

End point description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared ($\eta p^2$) provided an estimate of effect size with 95% confidence intervals (95% CI)

| End point type | Primary |
|---|---|

End point timeframe:

pre-ECT compared with with post-ECT4.
Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134

| End point values | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 19 | | |
| Units: MADRS score | | | | |
| arithmetic mean (standard deviation) | 23.81 (± 11.2) | 18.74 (± 9.44) | | |

**Statistical analyses**

| Statistical analysis title | ANCOVA - acute MADRS |
|---|---|

Statistical analysis description:

analysis of covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

| Comparison groups | Ketamine v Propofol |
|---|---|
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [7] |
| Method | ANCOVA |

Notes:

[7] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

**Primary: Hamilton Depression Rating Scale (HDRS) - Treatment effects analysis**

| End point title | Hamilton Depression Rating Scale (HDRS) - Treatment effects analysis |
|---|---|

End point description:

In a treatment effects analysis, linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT and 1-month assessments.

| End point type | Primary |
|---|---|

End point timeframe:

pre-ECT compared with those at post-final ECT and 1-month assessments.
Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134

| End point values | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 19 | | |
| Units: HDRS scores | | | | |
| arithmetic mean (standard deviation) | 13.50 (± 9.32) | 8.41 (± 4.70) | | |

**Statistical analyses**

| Statistical analysis title | Linear mixed model |
|---|---|

Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month

assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

| | |
|---|---|
| Comparison groups | Ketamine v Propofol |
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | > 0.05 [9] |
| Method | Mixed models analysis |

Notes:

[8] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

[9] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

## Primary: Montgomery Asberg Depression Rating Scale (MADRS) - Treatment effects analysis

| | |
|---|---|
| End point title | Montgomery Asberg Depression Rating Scale (MADRS) - Treatment effects analysis |

End point description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Pre-ECT compared to post-ECT and 1-month post-ECT
Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134

| **End point values** | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 19 | | |
| Units: MADRS score | | | | |
| arithmetic mean (standard deviation) | 18.69 (± 16.48) | 8.18 (± 6.27) | | |

## Statistical analyses

| **Statistical analysis title** | Linear mixed model - MADRS treatment effects |
|---|---|

Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

| | |
|---|---|
| Comparison groups | Ketamine v Propofol |

| | |
|---|---|
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | > 0.05 [11] |
| Method | Linear Mixed model |

Notes:

[10] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.
[11] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

## Secondary: Spatial Recognition Memory (SRM) - Acute analysis

| | |
|---|---|
| End point title | Spatial Recognition Memory (SRM) - Acute analysis |

End point description:

Analysis of Covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. Partial eta-squared ($\eta p^2$) provided an estimate of effect size with 95% confidence intervals (95% CI)

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

compared outcomes pre-ECT to post-ECT4
Means reported below are post-ECT4. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134

| **End point values** | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 19 | | |
| Units: Proportion correct | | | | |
| arithmetic mean (standard deviation) | 0.60 (± 0.12) | 0.63 (± 0.10) | | |

### Statistical analyses

| **Statistical analysis title** | ANCOVA - acute SRM |
|---|---|

Statistical analysis description:

analysis of covariance (ANCOVA) compared outcomes pre-ECT with post-ECT4. All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

| | |
|---|---|
| Comparison groups | Ketamine v Propofol |
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [12] |
| Method | ANCOVA |

Notes:

[12] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

## Secondary: Spatial Recognition Memory (SRM) - Treatment effects analysis

| | |
|---|---|
| End point title | Spatial Recognition Memory (SRM) - Treatment effects analysis |

End point description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-ECT compared with post-ECT and 1-month post-ECT.
Means reported below are post-ECT. For full table of mean scores please refer to accompanying paper: https://doi.org/10.1192/bjp.bp.116.189134

| **End point values** | Ketamine | Propofol | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 19 | | |
| Units: SRM proportion correct | | | | |
| arithmetic mean (standard deviation) | .60 (± .16) | .64 (± .11) | | |

## Statistical analyses

| **Statistical analysis title** | Linear mixed model - SRM treatment effects |
|---|---|

Statistical analysis description:

Linear mixed models compared outcomes assessed pre-ECT with those at post-final ECT & 1-month assessments. A compound symmetry (CS) covariance matrix was compared with a first-order autoregressive and an unstructured covariance matrix. Model fit was assessed using Akaike's Information Criterion (AIC). The better fitting model (smallest AIC) reported. This was the model with the CS covariance matrix. Estimation proceeded using restricted maximum likelihood to a maximum of 100 iterations.

| Comparison groups | Ketamine v Propofol |
|---|---|
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | > 0.05 [14] |
| Method | Linear Mixed model |

Notes:

[13] - All analyses were run with anaesthetic and time as fixed factors and anaesthetic x time as an interaction term. Age and gender were included as covariates.

[14] - This is main effect of anaesthetic group. For main effect of time and interaction between time and group please consult the published results paper.

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

up to 30 days after the participant completed or discontinued the study.

Adverse event reporting additional description:

The CI and sponsor informed within 24 hours of serious adverse events or reactions and follow up with a formal written report.
If a SUSAR is life threatening then the MHRA and REC will be notified within 7 days of the event occurring; if the SUSAR is not life threatening, then it will be reported within 15 days of the event occurring.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | No dictionary |
| Dictionary version | 00 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ketamine |
| Reporting group description: - | |
| Reporting group title | Propofol |
| Reporting group description: - | |

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: No non-serious adverse events were recorded during the course of the trial.

| Serious adverse events | Ketamine | Propofol | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Psychiatric disorders | | | |
| prolonged hospital admission | Additional description: a participant developed an elevated mood following their ECT course | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Ketamine | Propofol | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 October 2011 | Increase in time data held from 10 to 15 years from end of study. |
| 08 August 2013 | Change in definition of the sample from which participants can be recruited to add "We will also recruit in-patients who subsequently leave the hospital "on pass" between treatments (after appropriate medical assessment by their treating teams), and return to the hospital for ECT before going home on the same day."<br><br>Due to good recruitment (N = 35) with 9 months of recruitment remaining a change to target sample size from 40 to 50 was made.<br><br>A non-substantial amendment was later made in May 2014 reducing the target sample size back to 40. |

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.

The limitations of the EUdract system and the support provided mean that accurately representing the results within it was difficult. Readers are advised to read the open-access paper linked to this record for a full desciption of the analysis.

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/28254962