

# THE LANCET

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.  
We post it as supplied by the authors.

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# Emergency treatment with Levetiracetam or Phenytoin in convulsive status epilepticus in children – the EcLiPSE trial: Supplementary Material

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## 1. Primary outcome

### 1.1 Cox Proportional Hazards model (all children)

Unadjusted HRs

|                             | <b>Hazard ratio (95% confidence interval)</b> | <b>p-value</b> |
|-----------------------------|---|----------------|
| Levetiracetam vs. Phenytoin | 1.2 (95% CI 0.91-1.6)                         | P=0.2          |

Unadjusted Schoenfelds for primary outcome:

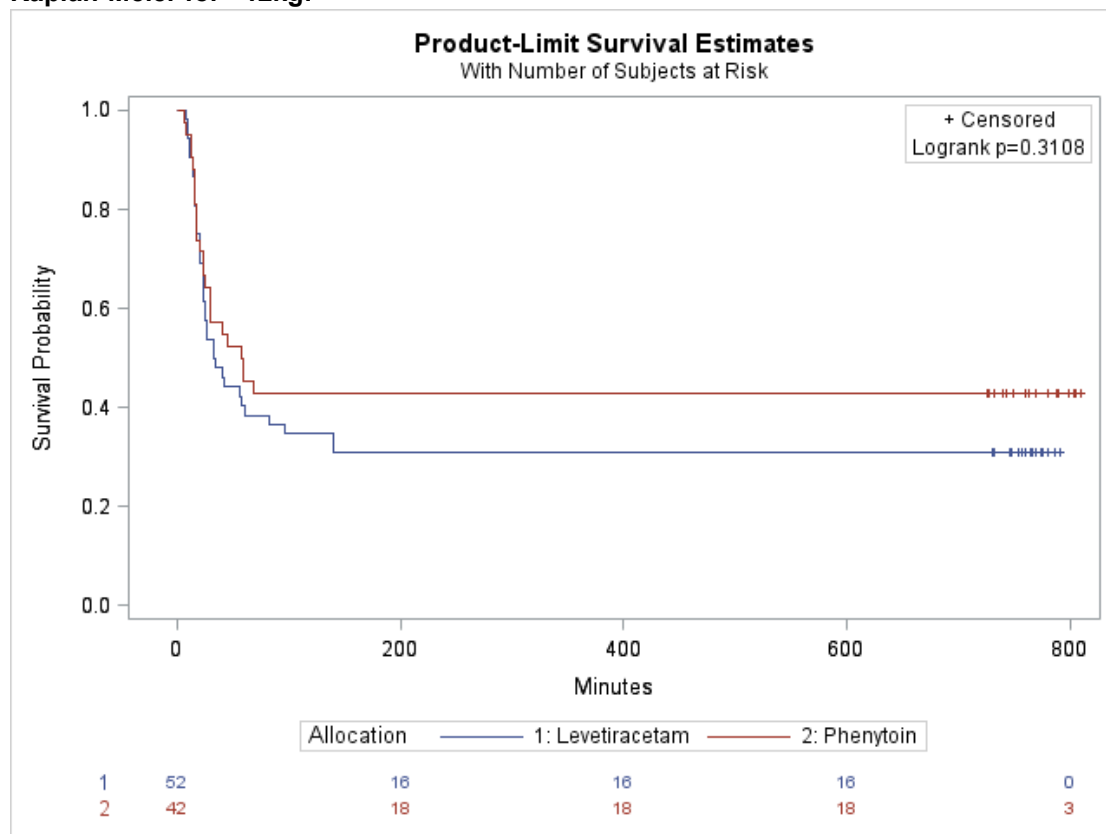
| <b>Supremum Test for Proportionals Hazards Assumption</b> |                               |                     |                          |
|---|-------------------------------|---------------------|--------------------------|
| <b>Variable</b>   | <b>Maximum Absolute Value</b> | <b>Replications</b> | <b>Pr &gt; MaxAbsVal</b> |
| Levetiracetam vs. Phenytoin                               | 0.6100                        | 1000                | 0.7200                   |

Adjusted Schoenfelds for primary outcome:

| <b>Supremum Test for Proportionals Hazards Assumption</b> |                               |                     |                          |
|---|-------------------------------|---------------------|--------------------------|
| <b>Variable</b>   | <b>Maximum Absolute Value</b> | <b>Replications</b> | <b>Pr &gt; MaxAbsVal</b> |
| Levetiracetam vs. Phenytoin                               | 0.6207                        | 1000                | 0.7100                   |
| Gender: Female vs Male                                    | 0.9470                        | 1000                | 0.2520                   |
| Weight  | 1.8151                        | 1000                | 0.0050                   |
| First seizure: No vs Yes                                  | 0.9665                        | 1000                | 0.2670                   |

## 1.2 Children with weight <12kg:

Kaplan-Meier for <12kg:



Unadjusted Schoenfelds for <12kg:

| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 0.4659                 | 1000         | 0.8870         |

Unadjusted HRs for <12kg:

|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.301 (0.776, 2.181)                   | 0.3185  |

Adjusted Schoenfelds for <12kg:

| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 0.4595                 | 1000         | 0.9040         |
| Gender: Female vs Male                             | 1.0542                 | 1000         | 0.1410         |
| Weight   | 1.2529                 | 1000         | 0.1400         |

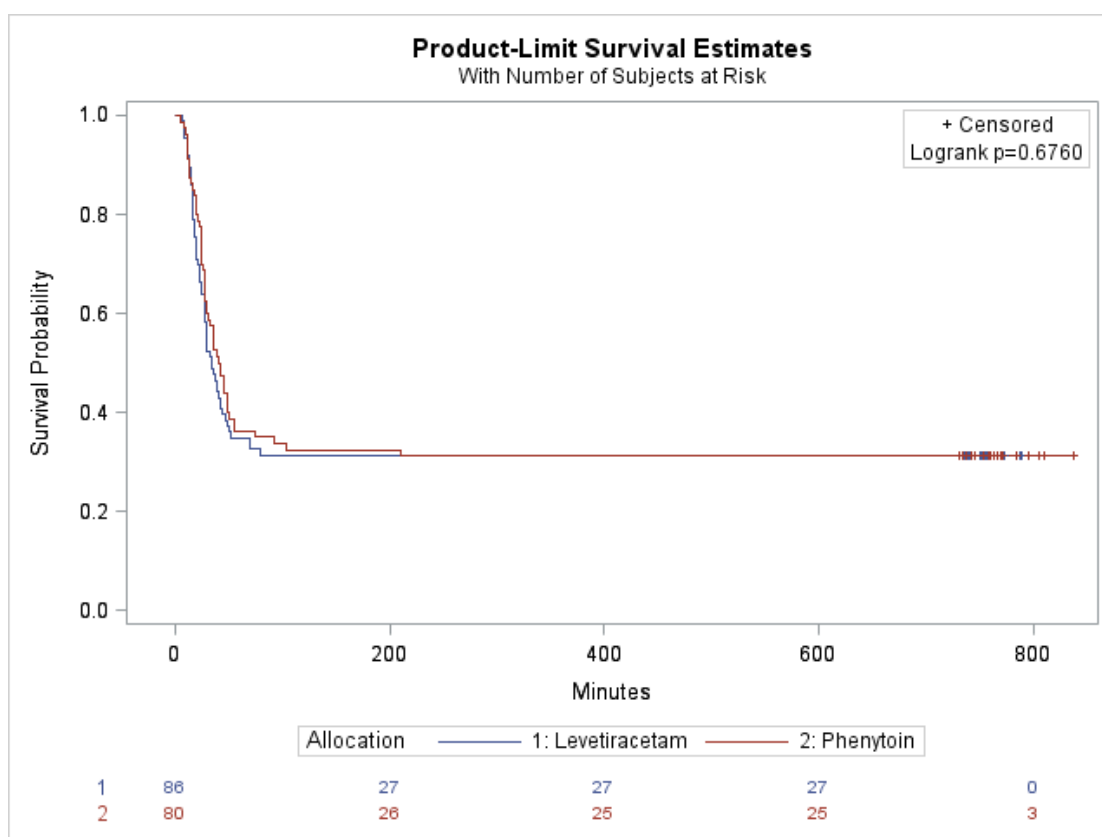
|                             |        |      |        |
|-----------------------------|--------|------|--------|
| First seizure:<br>No vs Yes | 0.8390 | 1000 | 0.2930 |
|-----------------------------|--------|------|--------|

Adjusted HR for <12kg:

|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.250 (0.737, 2.120)                   | 0.4087  |
| Gender: Female vs Male      | 1.020 (0.599, 1.736)                   | 0.9418  |
| Weight                      | 1.172 (0.873, 1.573)                   | 0.2910  |
| First seizure: No vs Yes    | 1.495 (0.862, 2.593)                   | 0.1526  |

### 1.3 Children with weight 12 to 36kg:

Kaplan-Meier for 12 to 36kg:



Unadjusted Schoenfelds for 12 to 36kg:

| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 0.7902                 | 1000         | 0.3950         |

Unadjusted HRs for 12 to 36kg:

|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.081 (0.748, 1.561)                   | 0.6791  |

Adjusted Schoenfelds for 12 to 36kg:

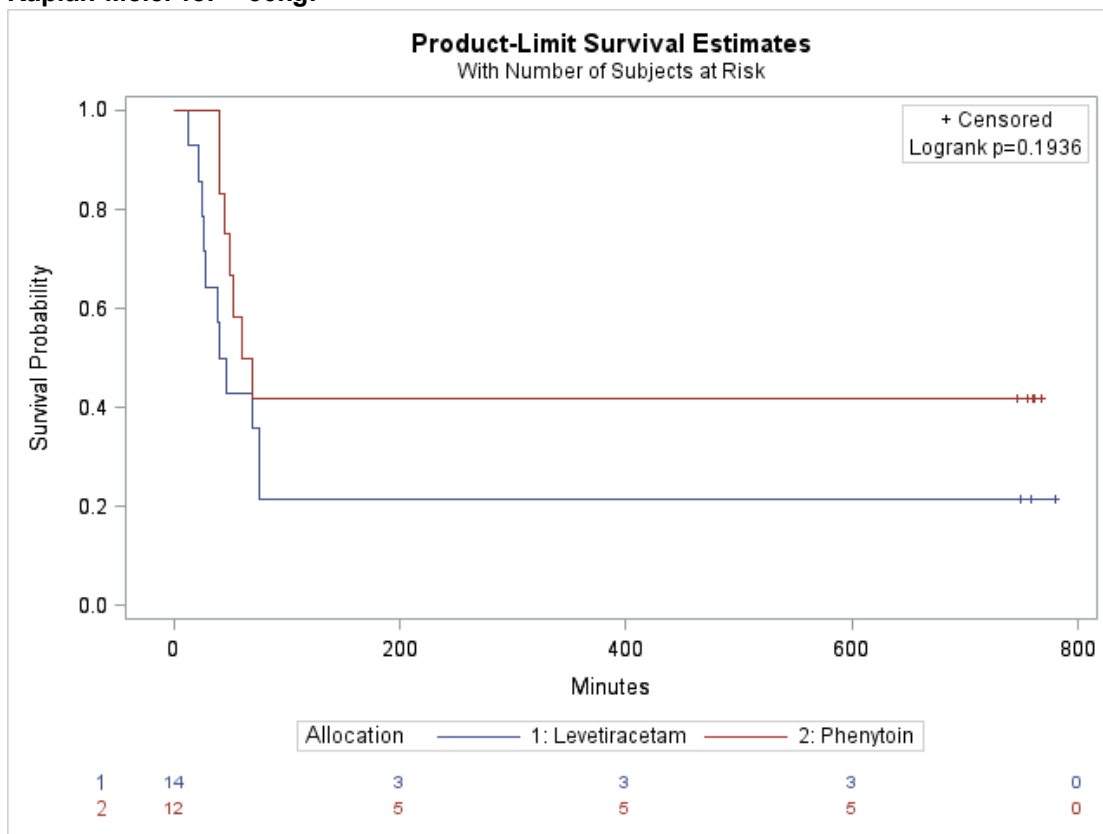
| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 0.8037                 | 1000         | 0.3870         |
| Gender: Female vs Male                             | 0.7263                 | 1000         | 0.5030         |
| Weight   | 0.9563                 | 1000         | 0.2280         |
| First seizure: No vs Yes                           | 0.7400                 | 1000         | 0.5240         |

Adjusted HR for 12 to 36kg:

|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.080 (0.742, 1.571)                   | 0.6886  |
| Gender: Female vs Male      | 1.036 (0.710, 1.511)                   | 0.8540  |
| Weight                      | 0.998 (0.968, 1.029)                   | 0.9047  |
| First seizure: No vs Yes    | 0.960 (0.629, 1.465)                   | 0.8497  |

### 1.4 Children with weight > 36kg category:

Kaplan-Meier for > 36kg:



Unadjusted Schoenfelds for > 36kg:

| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 1.0623                 | 1000         | 0.0910         |

Unadjusted HRs for > 36kg:

|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.845 (0.712, 4.781)                   | 0.2072  |

Adjusted Schoenfelds for > 36kg:

| Supremum Test for Proportionals Hazards Assumption |                        |              |                |
|--|------------------------|--------------|----------------|
| Variable   | Maximum Absolute Value | Replications | Pr > MaxAbsVal |
| Levetiracetam vs. Phenytoin                        | 1.1107                 | 1000         | 0.0860         |
| Gender: Female vs Male                             | 0.8301                 | 1000         | 0.5380         |
| Weight   | 0.7626                 | 1000         | 0.6220         |
| First seizure: No vs Yes                           | 0.8002                 | 1000         | 0.2320         |

Adjusted HR for > 36kg:

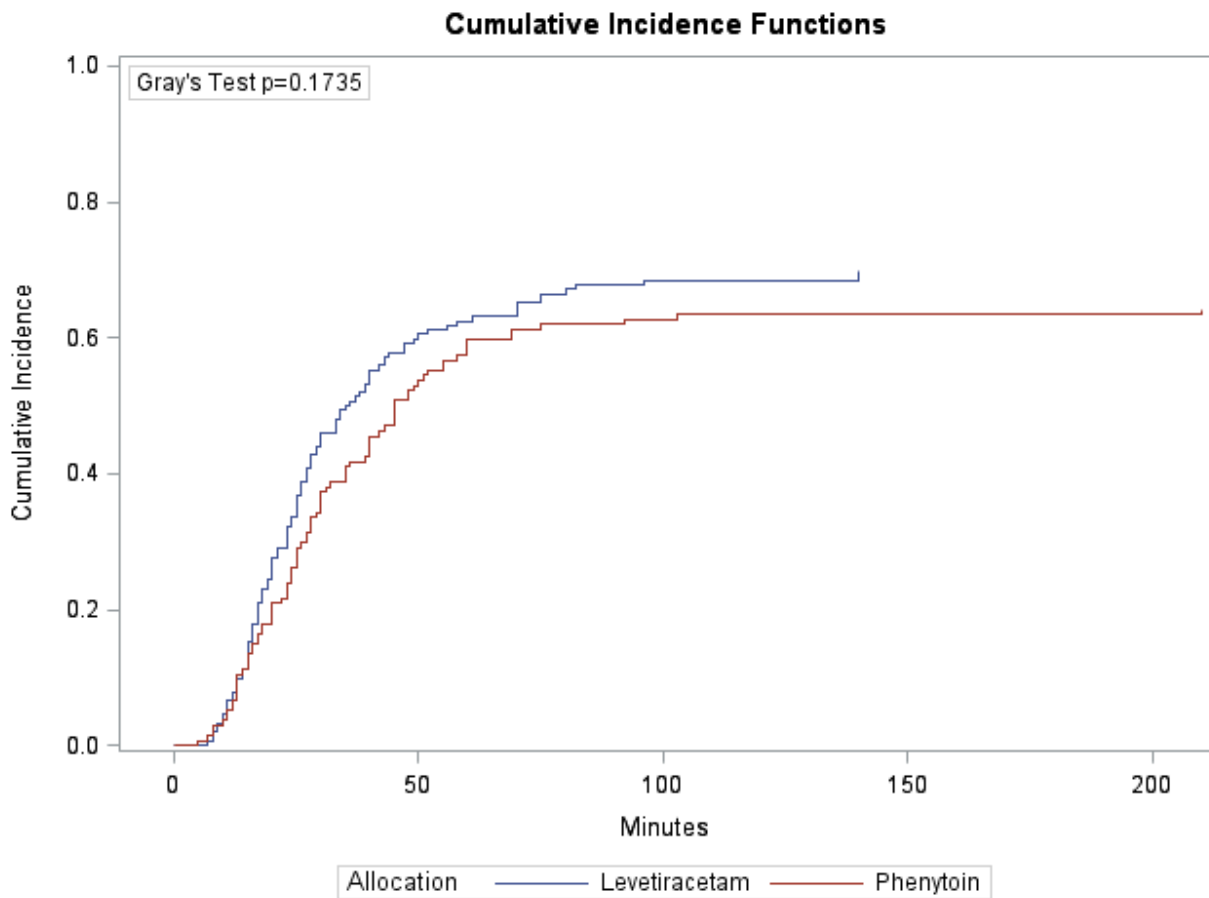
|                             | Hazard ratio (95% confidence interval) | p-value |
|-----------------------------|--|---------|
| Levetiracetam vs. Phenytoin | 1.690 (0.621, 4.599)                   | 0.3043  |
| Gender: Female vs Male      | 0.934 (0.276, 3.162)                   | 0.9128  |
| Weight                      | 1.039 (0.977, 1.104)                   | 0.2201  |
| First seizure: No vs Yes    | 2.084 (0.455, 9.538)                   | 0.3443  |

### 1.5 Time to seizure cessation using Gray's test for competing risks

Time to seizure cessation using Gray's test for competing risks

|   | Levetiracetam (N = 152) | Phenytoin (N = 134) |
|---|-------------------------|---------------------|
| Number of events of interest (seizure cessation), N (%) | 106 (69.74%)            | 86 (64.18%)         |
| Number of competing events (RSI), N (%)                 | 46 (30.26%)             | 48 (35.82%)         |

Cumulative Incidence Plot





**Time to seizure cessation using Gray's test for competing risks results (unadjusted Fine and Gray model)**

|                                    | <b>Subdistribution hazard ratio (95% confidence interval)</b> |                      | <b>p-value</b> |
|------------------------------------|---|----------------------|----------------|
| <b>Levetiracetam vs. Phenytoin</b> | HR for seizure cessation                                      | 1.202 (0.908, 1.592) | 0.1976         |
|                                    | HR for RSI  | 0.837 (0.560, 1.250) | 0.3843         |

**1.6 Time to seizure cessation from infusion**

**Time to seizure cessation from infusion**

|   | <b>Levetiracetam (N = 152)</b> | <b>Phenytoin (N = 134)</b> |
|---|--------------------------------|----------------------------|
| Number of events (seizure cessation), N (%)                               | 106 (69.74%)                   | 86 (64.18%)                |
| Number of censored times (RSI), N (%)                                     | 46 (30.26%)                    | 48 (35.82%)                |
| Median time to cessation of seizure from start of infusion, minutes (IQR) | 17.50 (8.00 – NA)              | 24.50 (8.00 – NA)          |

**Unadjusted Schoenfelds for Time to seizure cessation from infusion:**

| <b>Supremum Test for Proportionals Hazards Assumption</b> |                               |                     |                          |
|---|-------------------------------|---------------------|--------------------------|
| <b>Variable</b>   | <b>Maximum Absolute Value</b> | <b>Replications</b> | <b>Pr &gt; MaxAbsVal</b> |
| <b>Levetiracetam vs. Phenytoin</b>                        | 0.6704                        | 1000                | 0.5850                   |

**Time to seizure cessation from infusion results (unadjusted Cox-PH model)**

|                                    | <b>Hazard ratio (95% confidence interval)</b> | <b>p-value</b> |
|------------------------------------|---|----------------|
| <b>Levetiracetam vs. Phenytoin</b> | 1.153 (0.867, 1.532)                          | 0.3279         |

**1.7 Time to seizure cessation censoring at time of 2<sup>nd</sup> second-line treatment**

**Time to seizure cessation censoring at time of 2<sup>nd</sup> second-line treatment**

|   | <b>Levetiracetam (N = 152)</b> | <b>Phenytoin (N = 134)</b> |
|---|--------------------------------|----------------------------|
| Number of events (seizure cessation), N (%)   | 98 (64.47%)                    | 85 (63.43%)                |
| Number of censored times (RSI), N (%)   | 41 (26.97%)                    | 45 (33.58%)                |
| Number of censored times (2 <sup>nd</sup> second-line treatment), N (%)                               | 13 (8.55%)                     | 4 (2.99%)                  |
| Median time to cessation of censoring at time of 2 <sup>nd</sup> second-line treatment, minutes (IQR) | 35 (20 – NA <sup>a</sup> )     | 45 (24 – NA <sup>a</sup> ) |

Unadjusted Schoenfelds for Time to seizure cessation censoring at time of 2<sup>nd</sup> second-line treatment:

| <b>Supremum Test for Proportionals Hazards Assumption</b> |                               |                     |                          |
|---|-------------------------------|---------------------|--------------------------|
| <b>Variable</b>   | <b>Maximum Absolute Value</b> | <b>Replications</b> | <b>Pr &gt; MaxAbsVal</b> |
| <b>Levetiracetam vs. Phenytoin</b>                        | 0.8734                        | 1000                | 0.3200                   |

Time to seizure cessation censoring at time of 2<sup>nd</sup> second-line treatment results (unadjusted Cox-PH model)

|                                    | <b>Hazard ratio (95% confidence interval)</b> | <b>p-value</b> |
|------------------------------------|---|----------------|
| <b>Levetiracetam vs. Phenytoin</b> | 1.152 (0.861, 1.540)                          | 0.3412         |

## 1.8 Anticonvulsants given in parallel with trial treatment, seizure cessation, and rapid sequence induction

|   | Levetiracetam | Phenytoin | Total |
|---|---------------|-----------|-------|
| Anticonvulsants given in parallel           | 4             | 13        | 17    |
| Paraldehyde                                 | 3             | 9         | 12    |
| Lorazepam                                   | 0             | 1         | 1     |
| Midazolam                                   | 0             | 1         | 1     |
| Propofol                                    | 1             | 0         | 1     |
| Phenytoin top-up                            | 0             | 1         | 1     |
| Missing                                     | 0             | 1         | 1     |
| Seizure stopped                             | 106           | 86        | 192   |
| After 1 <sup>st</sup> second-line treatment | 95            | 85        | 180   |
| After 2 <sup>nd</sup> second-line treatment | 11            | 1         | 12    |
| RSI for any reason <sup>a</sup>             | 46            | 48        | 94    |

<sup>a</sup> Numbers requiring an RSI specifically to terminate ongoing CSE are presented in Table 3 of the main paper

## 1.9 Manufacturers of the treatments used in EcLiPSE

| Treatment     | Manufacturer<br>(Name based on electronic<br>Medicines Compendium [eMC]<br>website) | Marketing Authorisation<br>(MA) Holder<br>(Name quoted on eMC<br>website for MA Holder) | MA Holder<br>country |
|---------------|---|---|----------------------|
| Levetiracetam | Beacon Pharmaceuticals  | Beacon Pharmaceuticals Limited  | England              |
|               | Bowmed Ibisqus Limited  | Ibigen Srl  | Italy                |
|               | Consilient Health Ltd   | Hikma Farmacêutica (Portugal), S.A.   | Portugal             |
|               | Desitin Pharma Ltd  | Desitin Arzneimittel GmbH   | Germany              |
|               | Hospira UK Ltd  | Pfizer Europe MA EEIG   | Belgium              |
|               | UCB Pharma Limited  | UCB Pharma SA   | Belgium              |
|               | Wockhardt UK Ltd  | Wockhardt UK Ltd  | UK                   |
|               | Unknown   | Unknown   | Unknown              |
| Phenytoin     | Hospira UK Ltd  | Hospira UK Limited  | United Kingdom       |
|               | Pfizer Limited  | Pfizer Limited  | United Kingdom       |
|               | Unknown   | Hikma Farmacêutica (Portugal), SA   | Portugal             |
|               | Unknown   | Mercury Pharmaceuticals Ltd   | United Kingdom       |
|               | Unknown   | Unknown   | Unknown              |

Generic formulations with a MA were also permitted

## **2. EcLiPSE oversight committee members**

### **2.1 Independent Trial Steering Committee (TSC) members**

Professor Imti Choonara (Department of Child Health, University of Nottingham and Derbyshire Children's Hospital, Derby, UK); Professor Caroline Doré (The Comprehensive Clinical Trials Unit at UCL, London, UK); Michael J Barrett (Our Lady's Children's Hospital, Dublin, Ireland); Professor Ronan O'Sullivan (Cork University Hospital, Cork, Ireland); Gail Miller (Patient and Public Involvement [PPI] representative); Jane V Green (PPI representative); Denise L Bustany (PPI representative).

### **2.2 Independent Data and Safety Monitoring Committee (IDSMC) members**

Professor Steff C Lewis (Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, UK); Julie A Ellison (Mid Cheshire Hospitals NHS Foundation Trust, UK); Professor Tony G Marson (University of Liverpool and The Walton Centre NHS Foundation Trust, Liverpool, UK).

## **3. EcLiPSE trial Nurse Leadership Group**

Alder Hey Children's Hospital NHS Foundation Trust: Joanne Noblet, Elizabeth D Lee, Rachel Greenwood-Bibby.

Bristol Royal Hospital for Children: Sarah Potter, Alice Smith, Phoebe Mouldsdale, Holly R Lavigne-Smith.

## **4. Participating sites and investigators**

Addenbrookes Hospital, Cambridge University NHS Trust, UK: Matthew Pereira, Susie Hardwick

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Birmingham Children's Hospital, UK: Stuart Hartshorn, Louise Rogers, Juliet Hopkins  
Bristol Royal Hospital for Children, UK: Mark D Lyttle, Daphin Fernandez, Sarah Potter, Holly R Lavigne-Smith, Phoebe Mouldsdales, Alice Smith, Tracey Bingham

Chelsea & Westminster NHS Foundation Trust, London, UK: James Ross, Natasha Ramsey, Jo Hacking

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King's College Hospital, London, UK: Emer Sutherland, Fleur Cattle, Sinead Helyar, Paul Rizzo, Hannah Cotton

Leeds General Infirmary, Leeds, UK: Alice J Downes, Helen Mollard

Leicester Hospitals, Leicester, UK: Damian Roland, Felix Hay

Nottingham University Hospitals NHS Trust, Nottingham, UK: Chris Gough, Sonya Finucane

Royal Alexandra Children's Hospital, Brighton, UK: Catherine Bevan, Rebecca Ramsay, Emily Walton

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Royal Hospital for Children, Glasgow, UK: Vince Choudhery, Stewart MacLeod, Ashleigh Neil

Royal Hospital for Sick Children, Edinburgh, UK: Jen Browning, , Thom O'Neill, Julia Grahamslaw

Royal London Hospital, London, UK: Ami Parikh, Imogen Skene, Rhys Thomas

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St George's University Hospitals NHS Foundation Trust, London, UK: Yasser Iqbal, Sarah Rounding

University Hospital Crosshouse, Kilmarnock, UK: Joanne Mulligan, Claire Bell, Shona McLellan, Shona Leighton

University Hospital Lewisham, London, UK: Tina Sajjanhar, Maggie Nyirenda, Anastasia Alcock, Laura Crome, Neil Williamson

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Watford General Hospital, London, UK: Chaniyil A Ramesh, Solomon Kamal-Uddin

Western Sussex Hospitals NHS Foundation Trust, UK: Mike Linney, Katia Vamvakiti, Sharon Floyd, Gill Hobden