PREDICT Paediatric Research in Emergency Departments International Collaborative

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

Starship Children's Health

ConSEPT: **Con**vulsive **S**tatus **E**pilepticus **P**aediatric **T**rial

Stuart Dalziel, Professor of Emergency Medicine & Paediatrics,
University of Auckland and Starship Children's Hospital,
on behalf of the ConSEPT study investigators

CSE The problem: **C**onvulsive **S**tatus **E**pilepticus

CSE

- Most common life threatening neurological emergency in children
  - ~20/100,000 in children
  - ~50/100,000 in <1 year olds
- 2nd most common PICU admission in UK (5.6%)
- ½ previously normal
- Mortality ~3%

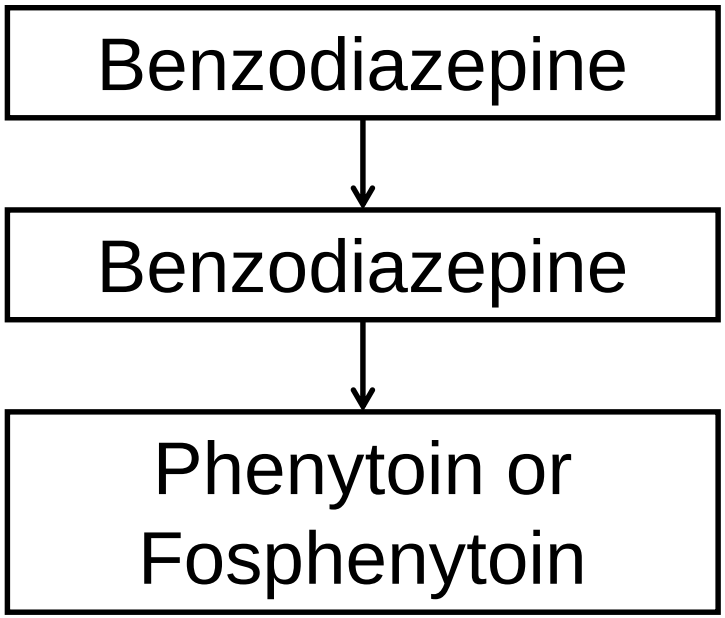
CSE The problem: **C**onvulsive **S**tatus **E**pilepticus

CSE management guidelines:

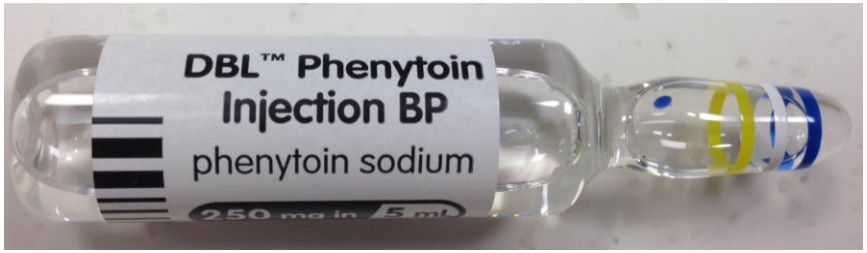
- Status Epilepticus Working Party UK (ADC 2000)
- SIGN (UK, 2005)
- APLS (UK and Australia & NZ, 2006)
- Textbook of Paediatric Emergency Medicine (Aus, 2018)
- Textbook of Pediatric Emergency Medicine (Fleisher & Ludwig, US, 2006)

CSE The problem: **C**onvulsive **S**tatus **E**pilepticus

CSE management guidelines:



CSE Evidence for phenytoin



Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children (Review)

Appleton R, Macleod S, Martland T

THE COCHRANE COLLABORATION®

- No trials of 2nd line anticonvulsants

CSE Evidence for phenytoin

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THE COCHRANE COLLABORATION®

SIGN
Scottish Intercollegiate Guidelines Network

NHS Quality Improvement Scotland

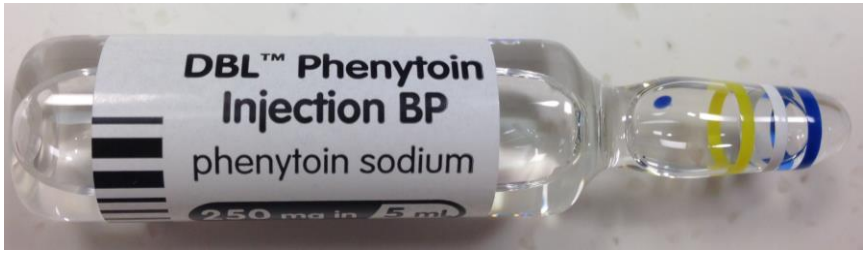
81 Diagnosis and management of epilepsies in children and young people
National clinical guideline

apls
ADVANCED PAEDIATRIC LIFE SUPPORT, N.Z. INC.

apls
Advanced Paediatric Life Support

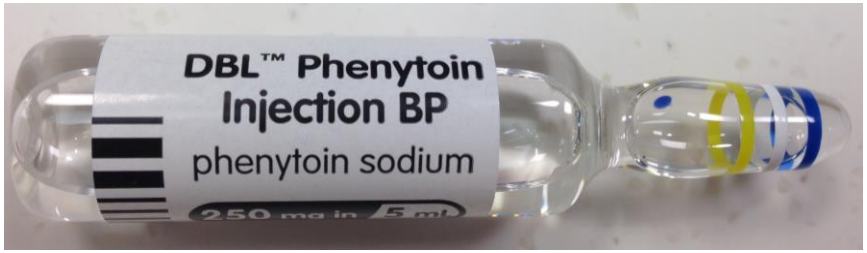
Level 4 evidence: Expert opinion

CSE How ideal is phenytoin?

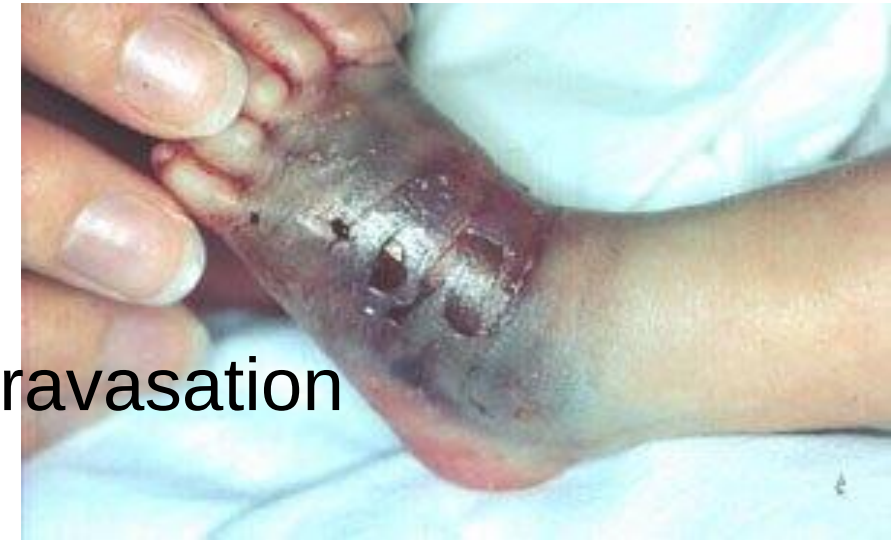


Efficacy = 60% (n=312 Lewena et al.)

CSE How ideal is phenytoin?



- ↓ levels of a number of AEDs (inducers P450)
- Hepatotoxicity
- Pancytopenia
- Stevens Johnson syndrome
- Cardiac arrhythmias
- Hypotension
- Phelebitis
- Purple glove syndrome
- Soft tissue injury from extravasation



CSE Levetiracetam an alternative to phenytoin?

Broad spectrum AED

Rapid - 5 min infusion

Safe (Gustafson 2007)

CSE Levetiracetam an alternative to phenytoin?

Efficacy = 80% (small cohort studies)

ConSEPT **Con**vulsive **S**tatus **E**pilepticus **P**aediatric **T**rial

- Aim
  - To determine whether IV levetiracetam (40mg/kg, max 3g) or IV phenytoin (20mg/kg, max 1g) is the better second line treatment for CSE in children

ConSEPT **Con**vulsive **S**tatus **E**pilepticus **P**aediatric **T**rial

- Aim
  - To determine whether IV levetiracetam (40mg/kg, max 3g) or IV phenytoin (20mg/kg, max 1g) is the better second line treatment for CSE in children

- Design
  - An open label randomised controlled trial in children presenting to EDs with CSE who were still seizing after 2 doses of benzodiazepines

ConSEPT Inclusion/exclusion

- Inclusion criteria
  1. Children aged between 3 months and 16 years
  2. CSE having failed benzodiazepines

ConSEPT Inclusion/exclusion

- Exclusion criteria
  1. Current levetiracetam or phenytoin use
  2. Previous administration of 2nd line anticonvulsants prior to ED arrival
  3. Allergic to medications
  4. Specific CSE management plan stating refractory to phenytoin
  5. Pregnancy
  6. Major head injury
  7. Previous enrollment

ConSEPT 13 sites

Townsville Hospital (QLD)

Lady Cilento Children's Hospital (QLD)

Gold Coast University Hospital (QLD)

John Hunter Hospital (NSW)

Children's Hospital Westmead (NSW)

Sydney Children's Hospital (NSW)

Royal Children's Hospital (VIC)

Monash Medical Centre (VIC)

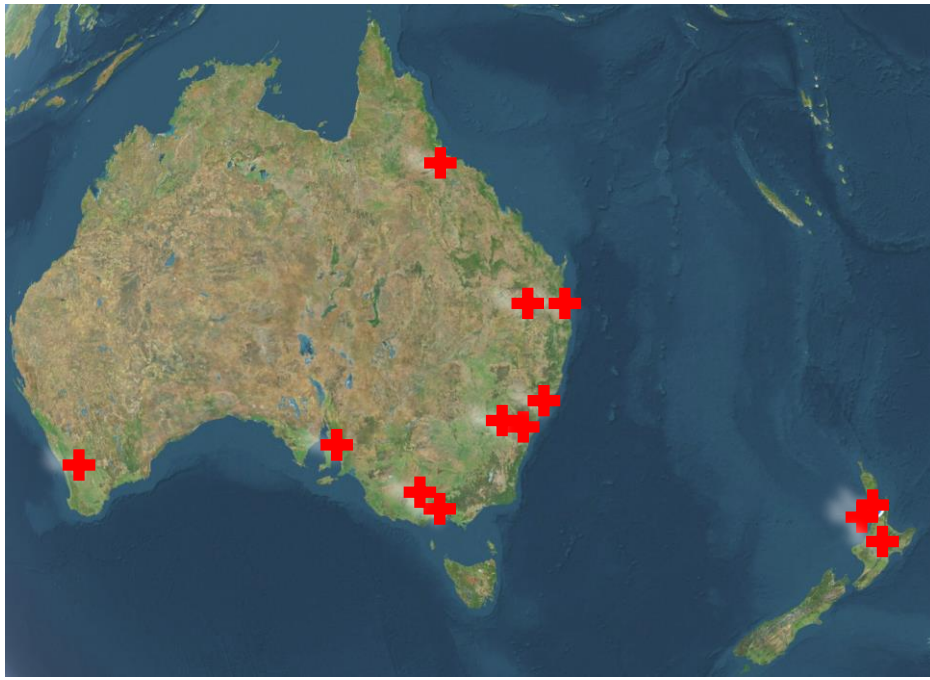
Women's and Children's Hospital (SA)

Princess Margaret Hospital (WA)

Starship Children's Hospital (NZ)

Kidzfirst Hospital (NZ)

Waikato Hospital (NZ)



PREDICT

ConSEPT Outcome

- Primary outcome
  - Clinical cessation of seizure activity; termination of seizure activity such that the treating physician considers the participant is no longer demonstrating abnormality of movement or tone
  - Videos used for robustness
- Power
  - 80% power to detect a total difference in seizure cessation rates between levetiracetam and phenytoin of 20% (alpha=0.05)

ConSEPT Outcome

- Secondary outcomes
  - Termination of seizure activity at 2 hours
  - Time to termination of seizure activity
  - Need for RSI
  - ICU admission
  - Length of Hospital/ICU stay
  - Health care costs
  - Serious adverse events
  - Follow-up at one month

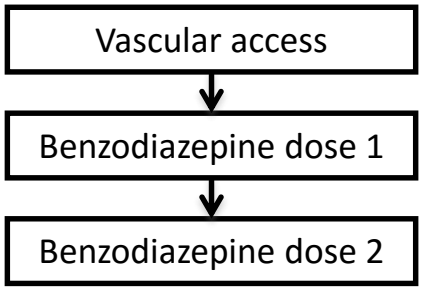
ConSEPT Flow

-15 min

-10 min

-5 min

0 min



PREDICT

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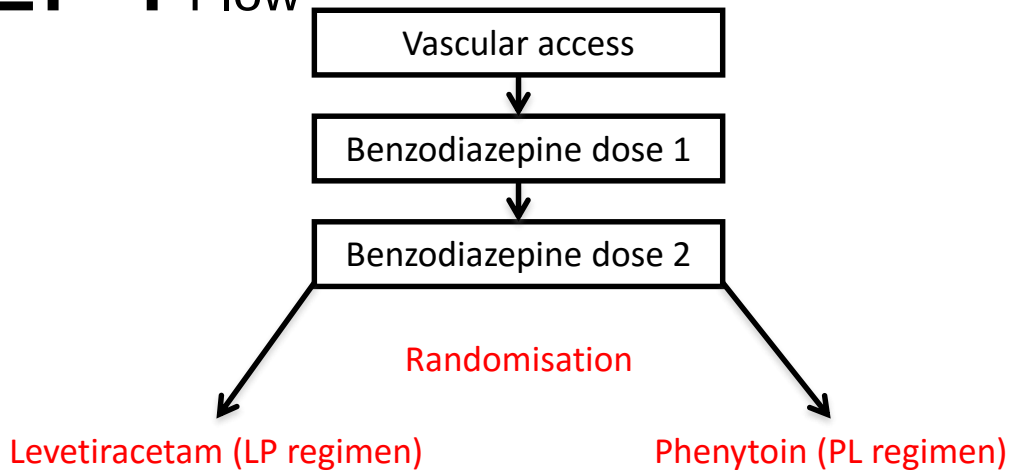

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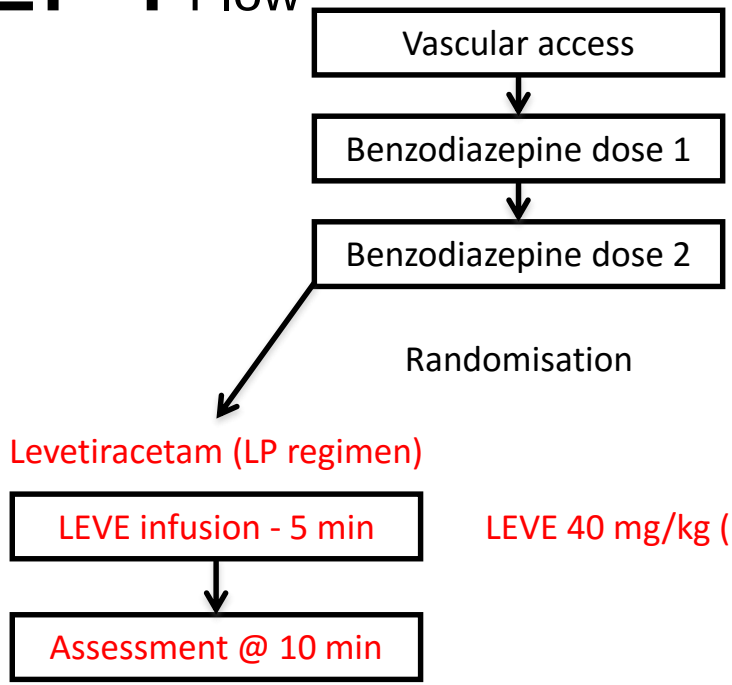


LEVE 40 mg/kg (max 3g)

+10 min
Primary outcome assessment for levetiracetam

ConSEPT Flow

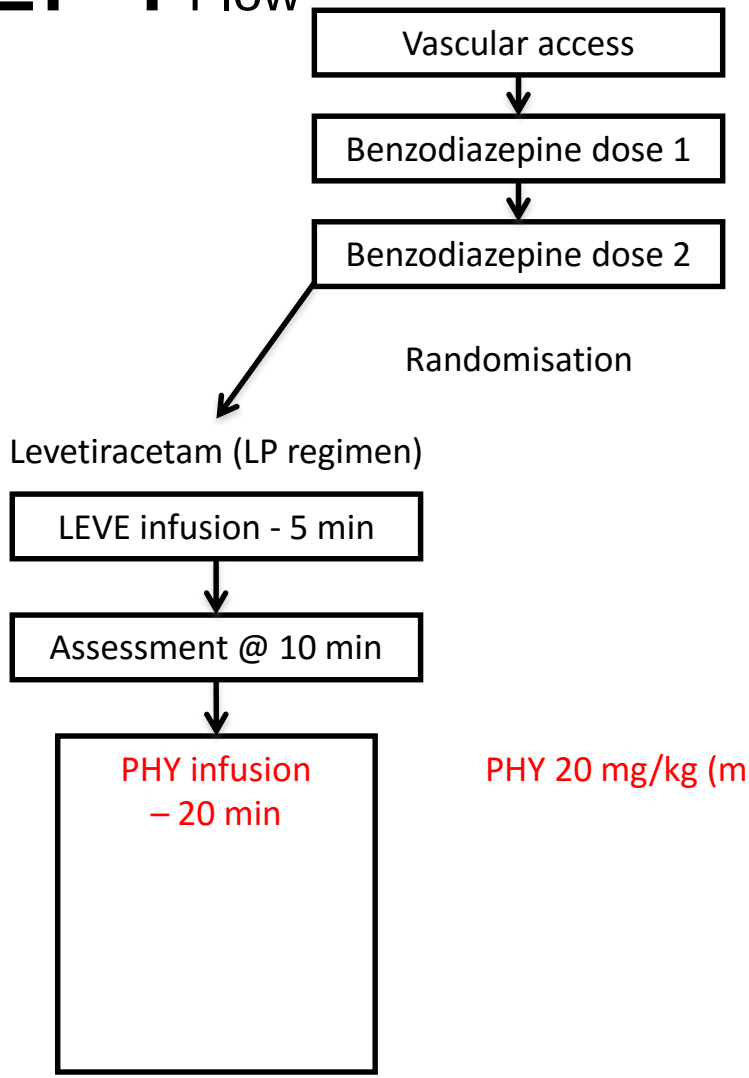
-15 min

-10 min

-5 min

0 min

+10 min
Primary outcome assessment for levetiracetam



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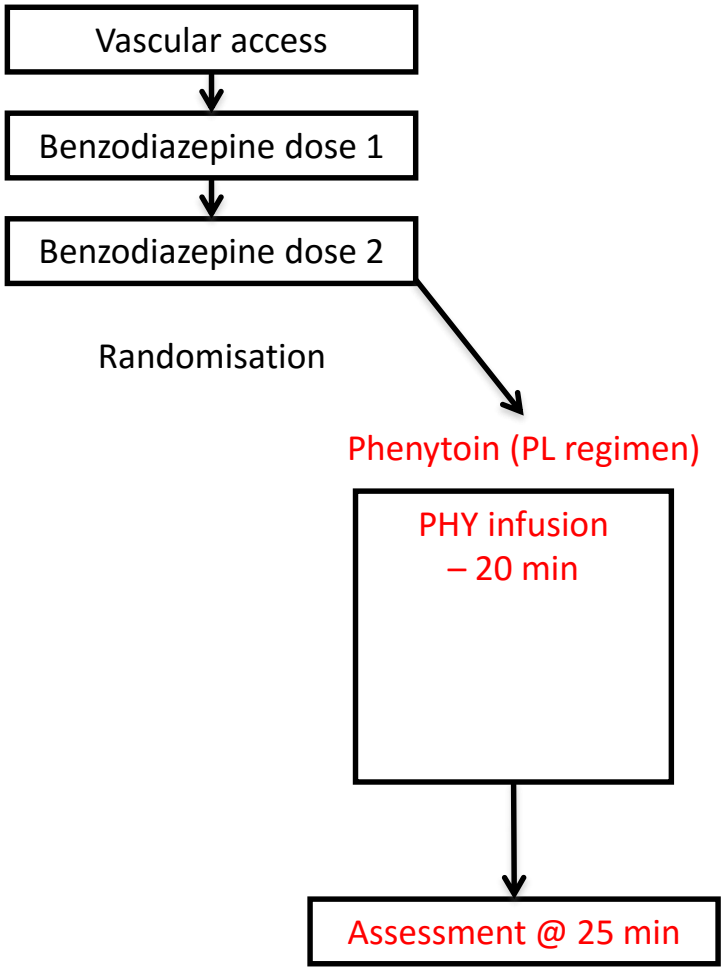


+25 min
Primary
outcome
assessment for
Phenytoin

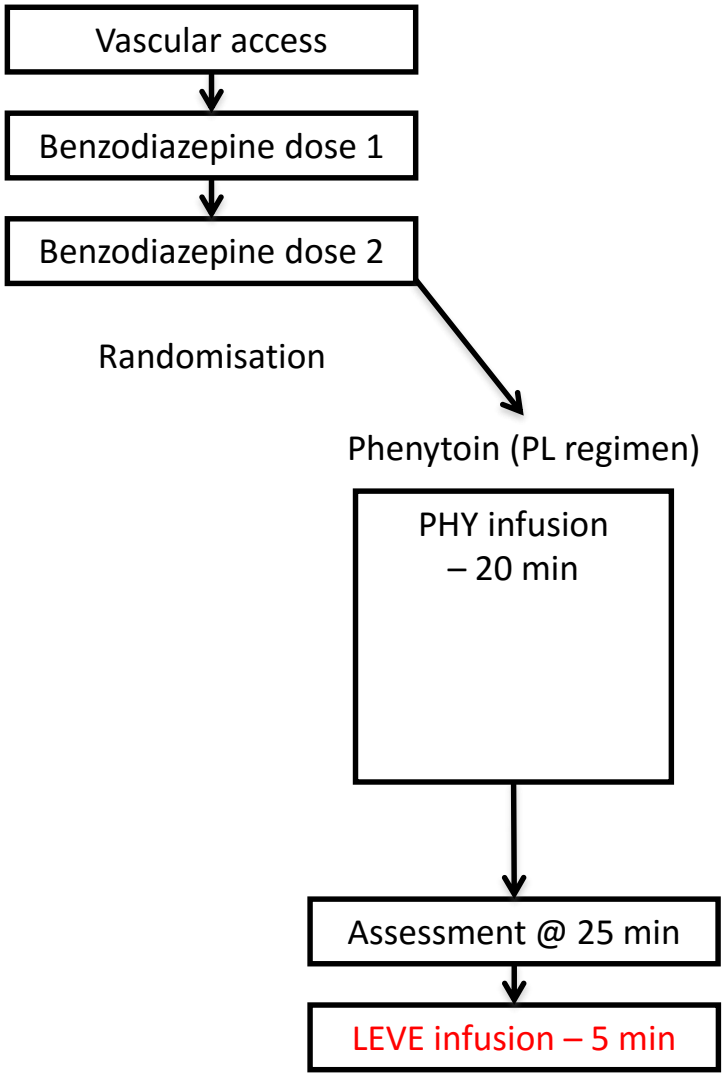
ConSEPT Flow

-15 min

-10 min

-5 min

0 min



+25 min
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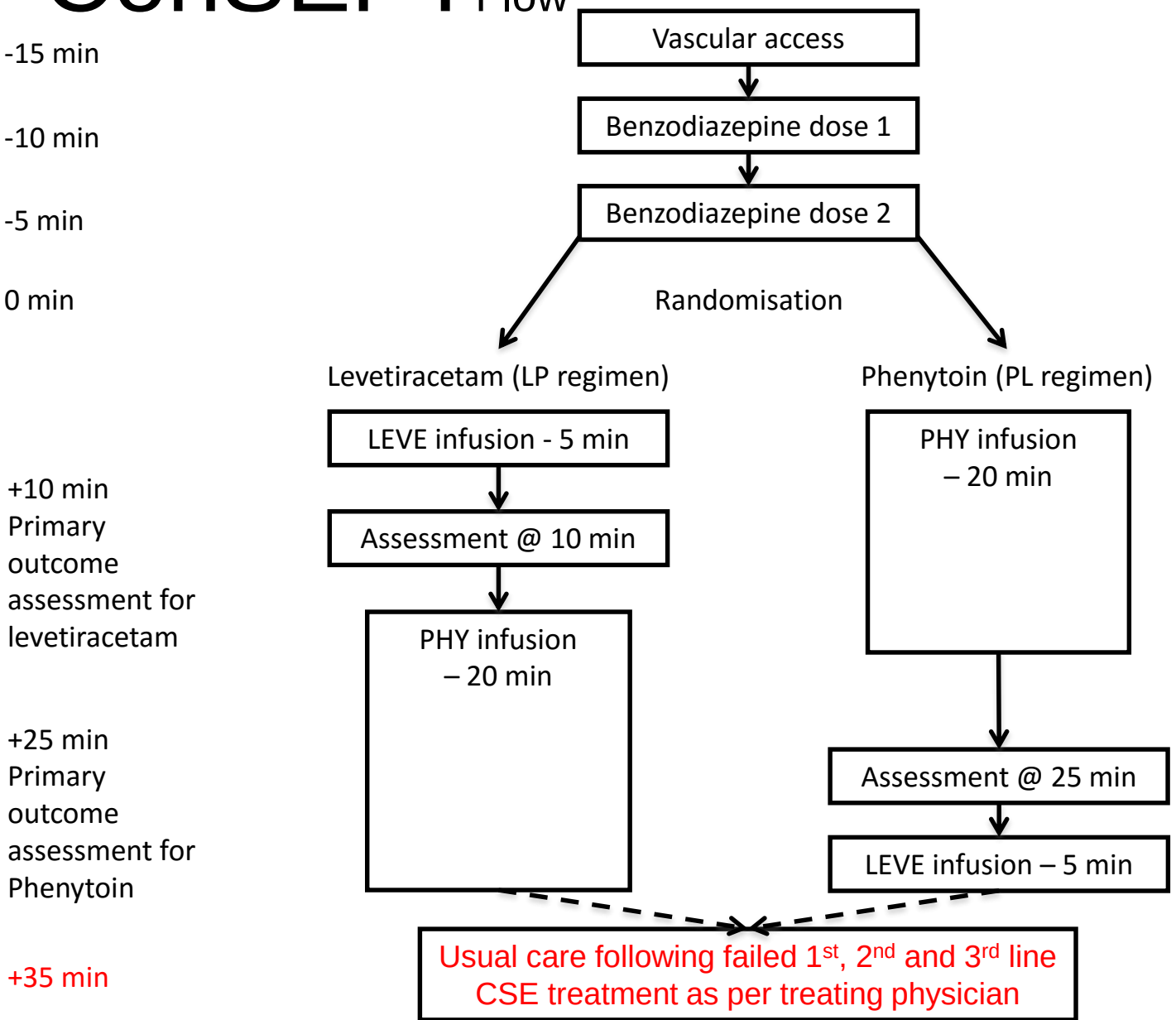
PREDICT

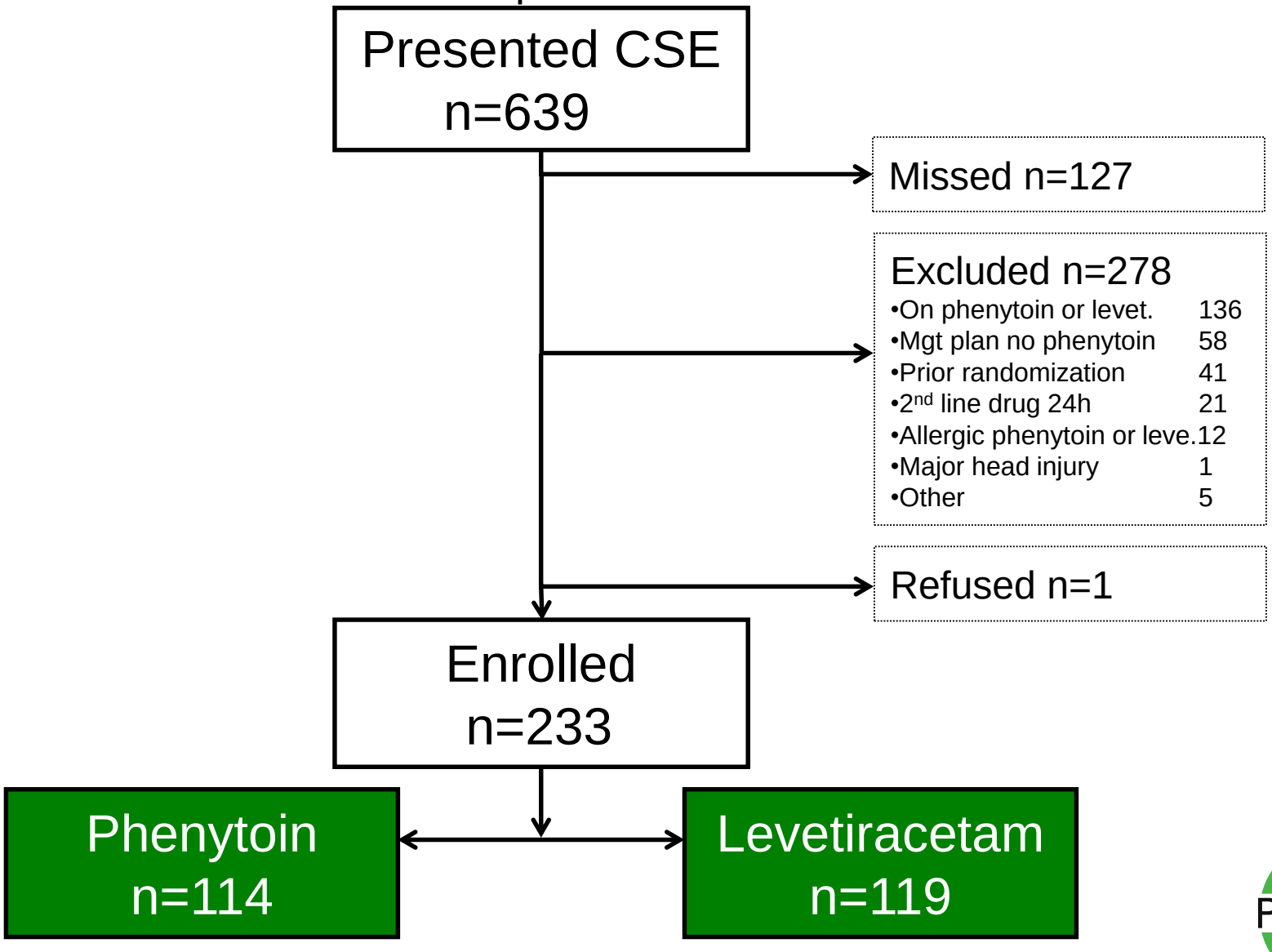
ConSEPT Flow



ConSEPT Consent

- Retrospective
- Written informed consent to remain in the study sought at the earliest possible time after emergency stabilisation of the CSE

ConSEPT Participant flow



ConSEPT Baseline characteristics

Table. Characteristics of randomised participants.

Characteristic	**Phenytoin** (n = 114)	**Levetiracetam** (n = 119)
Age		
Mean ± SD, y	4.0 ± 3.9	3.8 ± 3.8
Distribution - no. (%)		
≤ 5 y	82 (71.9)	85 (71.4)
> 5 y	32 (28.1)	34 (28.5)

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Male - no. (%)	53 (46.5)	59 (49.6)

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Male - no. (%)	53 (46.5)	59 (49.6)
Race or ethnic group - no. (%)		
New Zealand or Australian European	55 (48.2)	56 (47.1)
Aboriginal or Torres Strait Islander	3 (2.6)	4 (3.4)
Māori or Pacific Islander	16 (14.0)	20 (16.8)
Other	40 (35.1)	39 (32.8)

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Other	40 (35.1)	39 (32.8)
Medical history - no. (%)		
Premature birth	22 (19.3)	21 (17.6)
Traumatic brain injury	1 (0.9)	3 (2.5)
Cerebral palsy	11 (9.6)	7 (5.9)
Developmental delay	28 (24.6)	32 (26.9)
Congenital heart disease	6 (5.3)	6 (5.0)
Previous seizures	55 (48.2)	54 (45.4)
Previous status epilepticus	26 (22.8)	30 (25.2)
Regular anti-convulsant medication use	22 (19.3)	23 (19.3)

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ConSEPT Baseline characteristics

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Characteristic	**Phenytoin** (n = 114)	**Levetiracetam** (n = 119)
Family medical history		
Family history of seizures - no. (%)	24(21.1)	29 (24.4)
History of current status epilepticus presentation		
Febrile - no. (%)	82 (71.9)	87 (73.1)
Focal onset - no. (%)	14 (12.3)	14 (11.8)
Length of seizure prior to 1st study med – median (95% CI), h	1.2 (1.1-1.4)	1.2 (1.1-1.4)

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Focal onset - no. (%)	14 (12.3)	14 (11.8)
Length of seizure prior to 1st study med – median (95% CI), h	1.2 (1.1-1.4)	1.2 (1.1-1.4)
Clinical management prior to starting first study medication - no. (%)		
Midazolam used as first line anti-convulsant	105 (92.1)	112 (94.1)
Manual airway repositioning	75 (65.8)	87 (73.1)
Oral or nasal airway placement	13 (11.4)	18 (15.1)
Positive pressure ventilation	37 (32.5)	40 (33.6)
Tracheal intubation	3 (2.6)	2 (1.7)
Fluid bolus	21 (18.4)	28 (23.5)
Cardiac compression/defibrillation	0	0

PREDICT

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PREDICT

ConSEPT Primary outcome

Table. Primary efficacy outcome.

Outcome	Phenytoin (n=114)	Levetiracetam (n=119)	Relative risk (95% CI)	P value
Clinical cessation of seizure activity @ 5 min (ITT) - no. (%)	68 (59.6)	60 (50.4)	0.84 (0.66 to 1.07)	0.16
Clinical cessation of seizure activity @ 5 min (mITT)* - no. (%)	53 (55.2)	46 (45.5)	0.82 (0.62 to 1.10)	0.18
Clinical cessation of seizure activity @ 5 min (PPP)† - no. (%)	67 (60.4)	59 (50.4)	0.83 (0.66 to 1.06)	0.13

ITT = intention-to-treat

*mITT = modified intention-to-treat; excluding participants whose seizure activity stopped prior to the start of the first study medication.

†PPP = per-protocol-population; excluding participants who were intubated prior to to the start of the first study medication.

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No difference by age, focal vs. generalised CSE, febrile vs. afebrile, type of benzo.

PREDICT

ConSEPT Secondary outcomes

Table. Secondary efficacy outcomes.

Outcome	Phenytoin (n=114)	Levetiracetam (n=119)
Clinical cessation of seizure activity @ 2 h no further treatment - no. (%)	62 (54.4)	61 (51.3)
Received alternative study medication in first 2 h - no. (%)	42 (36.8)	48 (40.3)
Clinical cessation of seizure activity @ 2 h following either P/PL or L/LP, no further treatment - no. (%)	89 (78.1)	86 (72.3)
Time to clinical seizure cessation from commencement of first study medication – median (95% CI), h	0.4 (0.3-0.6)	0.3 (0.2-0.4)

P > 0.05

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Time to clinical seizure cessation from commencement of first study medication – median (95% CI), h	0.4 (0.3-0.6)	0.3 (0.2-0.4)

P > 0.05

ConSEPT Secondary outcomes

Table. Secondary efficacy outcomes.

Outcome	Phenytoin (n=114)	Levetiracetam (n=119)
Intubation - n (%)		
Prior to first study medication	3 (2.6)	2 (1.7)
Within first 2 h	13 (11.4)	21 (17.6)
Subsequently during admission	5 (4.3)	8 (6.7)
Total	21(18.4)	31 (26.1)
Intensive care admission - no. (%)	34 (29.8)	39 (32.8)
Length of intensive care admission† - median (95% CI), h	20 (15.1-26.5)	32 (22.7-53.4)
Length of hospital admission‡ - median (95% CI), h	47 (43.6-58.9)	50 (45.7-53.8)

P > 0.05

PREDICT

ConSEPT Safety outcomes

Table. Safety outcomes.

Outcome	Phenytoin (n=114)	Levetiracetam (n=119)
Adverse events in first 2 h - no. (%)		
Death	0 (0.0)	0 (0.0)
Manual airway repositioning	42 (36.8)	45 (37.8)
Oral or nasal airway placement	4 (3.5)	9 (7.6)
Positive pressure ventilation	19 (16.7)	30 (25.2)
Tracheal intubation	13 (11.4)	21 (17.6)
Fluid bolus	33 (28.9)	41 (34.5)
Cardiac chest compressions	1 (0.9)	0 (0.0)
Cardiac defibrillation	0 (0.0)	0 (0.0)
Allergic reaction	4 (3.5)	0 (0.0)
Extravasation of intravenous or intraoseous infusions	3 (2.6)	1 (0.8)
Purple glove syndrome	1 (0.9)	0 (0.0)
Other	6 (5.3)	2 (1.7)
Serious adverse events in the first 2 h - no. (%)	42 (36.8)	55 (46.2)

P > 0.05

ConSEPT Follow-up at 1 month

Table. Follow-up at 1 month.

Outcome	Phenytoin (n=114)	Levetiracetam (n=119)
Death - n (%)	1 (0.8)	0 (0.0)
	(n=100)	**(n=100)**
Regular anti-convulsant medications - n (%)	43 (43.0)	40 (40.0)
Seizures since discharge - n (%)		
Nil	74 (74.0)	78 (78.0)
Daily	5 (5.0)	3 (3.0)
Weekly	4 (4.0)	5 (5.0)
< Weekly	9 (9.0)	9 (9.0)
Unknown	8 (8.0)	5 (5.0)
Further episode of status epilepticus - n (%)	9 (9.0)	6 (6.0)

P > 0.05

ConSEPT Limitations

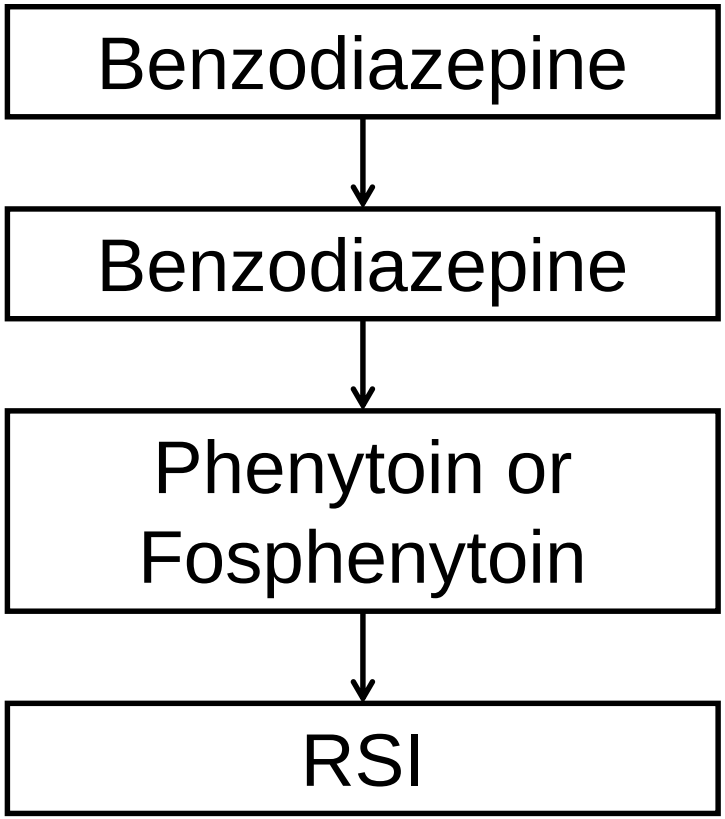
- Open design
  - Video assessment in 66%
- No EEG confirmation of CSE or cessation
  - Pseudo-seizures & seizure mimics may be included
  - But reflects ED environment
- Different timing of primary outcome assessment
- Excluded those on levetiracetam

ConSEPT Summary

- No difference in seizure cessation
  - Post infusion PHY vs. LEVE
  - At 2 hours post PHY vs. LEVE
  - At 2 hours post P/P+L vs. L/L+P
- No difference in adverse events
- No difference in LOS or ICU admission
- No difference in time to cessation
- Levetiracetam is not superior to Phenytoin for second line management of CSE

ConSEPT Discussion

In refractory CSE time to seizure cessation (RSI) important



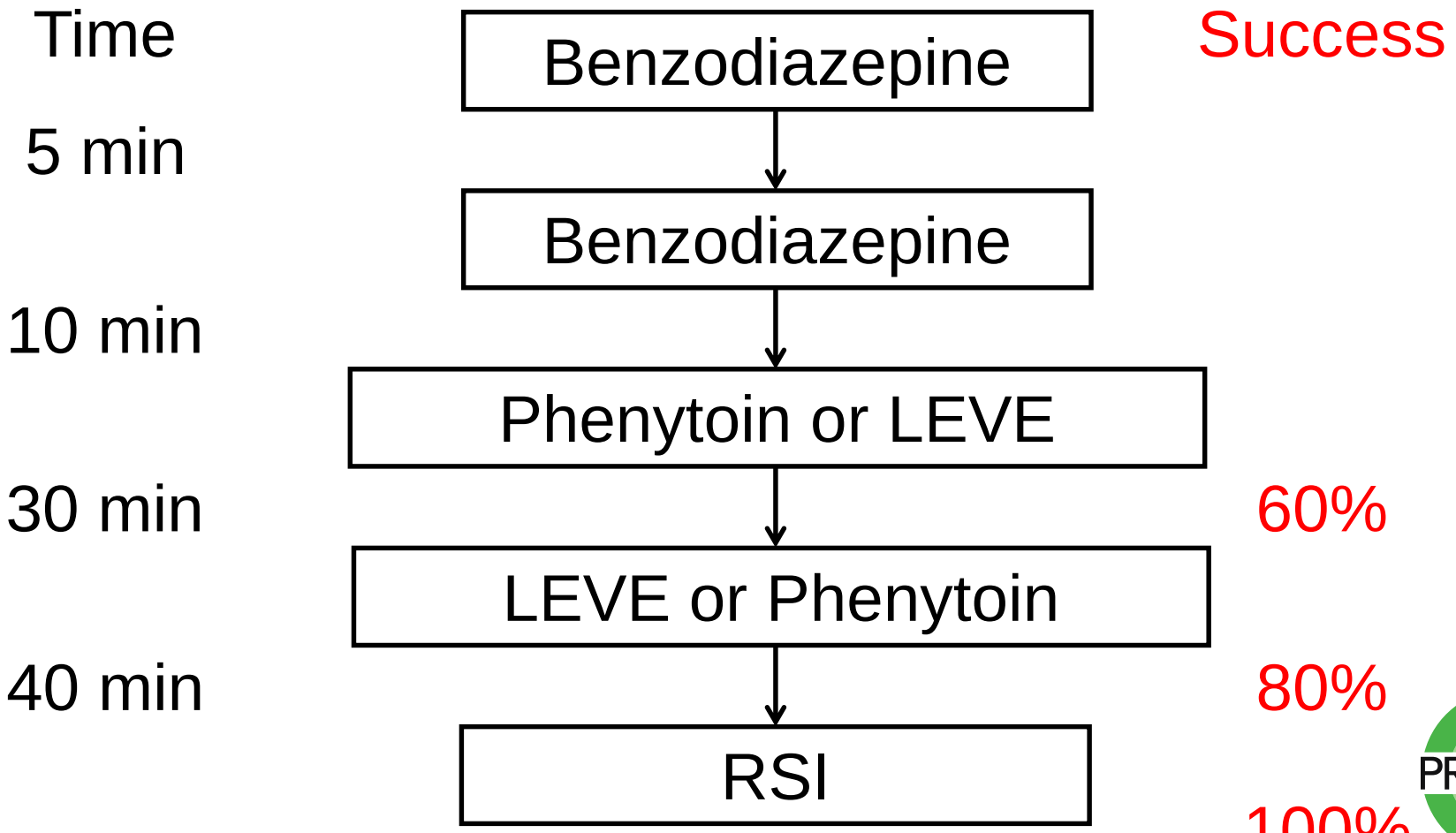
ConSEPT Discussion

- RSI not without adverse events & increased resources

- In ConSEPT
  - 40% failed phenytoin
  - Of these 46 participants 27 (59%) were managed with just levetiracetam

ConSEPT Discussion

Possible treatment



ConSEPT Discussion

Cochrane

Lyttle *et al. Trials* (2017) 18:283
DOI 10.1186/s13063-017-2010-8

Trials

STUDY PROTOCOL Open Access

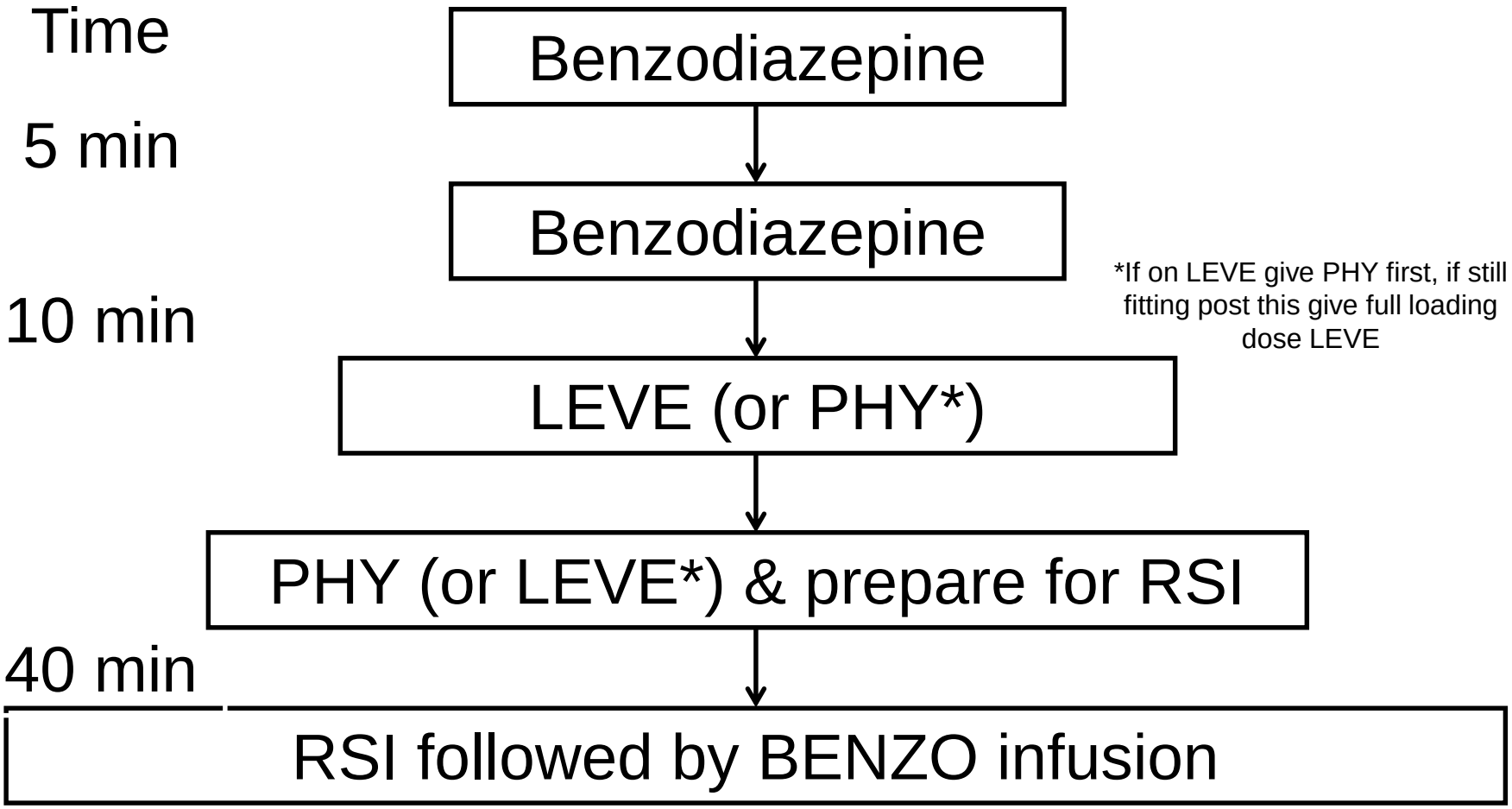
Emergency treatment with levetiracetam or phenytoin in status epilepticus in children—the EcLiPSE study: study protocol for a randomised controlled trial

Mark D. Lyttle[1,2], Carrol Gamble[3], Shrouk Messahel[4], Helen Hickey[5], Anand Iyer[4], Kerry Woolfall[6], Amy Humphreys[5], Naomi E. A. Bacon[3], Louise Roper[6], Franz E. Babl[7,8,9], Stuart R. Dalziel[10,11], Mary Ryan[4], Richard E. Appleton[4*]
and supported by Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI)

ESETT

PREDICT

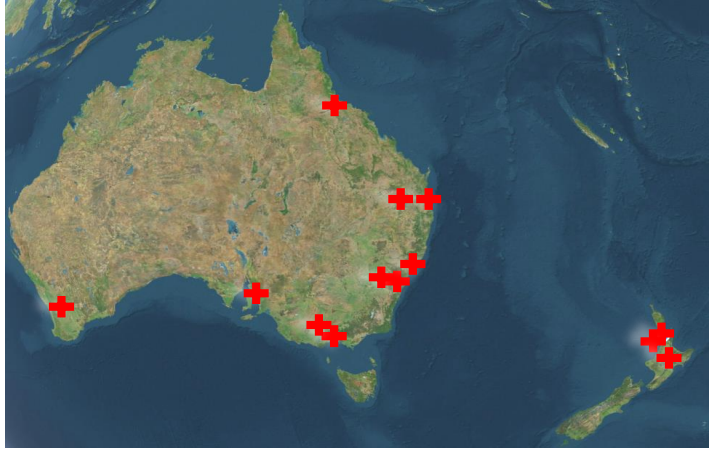
Starship guidelines



Starship guidelines

- Benefits
  - Avoids phenytoin in >50% of the children
  - Phenytoin has lead to deaths due to rate and dosing errors
  - By giving two medications quickly we reduce the “intubation rate” from 40% to 20% at the expense of 10 min
  - By giving phenytoin second it allows time to prepare for RSI
  - Allows timely RSI
  - Clear instructions what to do next

ConSEPT Acknowledgements



Patients, families & staff

- **Investigators & coordinators**
  - Megan Bonisch, Cia Sharpe, Starship Children's Hospital, Auckland, NZ
  - Jocelyn Neutze, Shirley Lawrence, Kidz First Hospital, Auckland, NZ
  - Christine Brabyn, Waikato Hospital, Hamilton, NZ
  - Franz Babl, Ed Oakley, Kate Francis, Susan Donath, Andrew Davidson, Simon Harvey, Amanda Williams, RCH, Melbourne, VIC
  - Meredith Borland, Sharon O'Brien, Princess Margaret Hospital, Perth, WA
  - Jeremy Furyk, Susan Montgomery, Leorie Jones, Townsville Hospital, Townsville, QLD
  - Natalie Phillips, Gabrielle Van Andel, Lady Cilento Children's Hospital, Brisbane, QLD
  - Simon Craig, Kathryn Wilson, Emma Ramage, Monash Medical Centre, Melbourne, VIC
  - Shane George, Gold Coast University Hospital, Southport, QLD
  - Michael Zhang, John Hunter Hospital, Newcastle, NSW
  - Arjun Rao, Yvonne Janiszewshi, Sydney Children's Hospital, Sydney, NSW
  - Nicholas Cheng, Deepali Thosar, Children's Hospital Westmead, Sydney, NSW
  - Amit Kochar, Gaby Nieva, Women's and Children's Hospital, Adelaide, SA
- **Funding**
  - Health Research Council of New Zealand (HRC 12/525) NZ; A+ Trust (Auckland District Health Board) NZ; Queensland Emergency Medicine Research Foundation QLD; Private Practice Research and Education Trust Fund QLD; Eric Ormond Baker Charitable Fund VIC; and Princess Margaret Hospital Foundation WA.

PREDICT

ConSEPT Questions