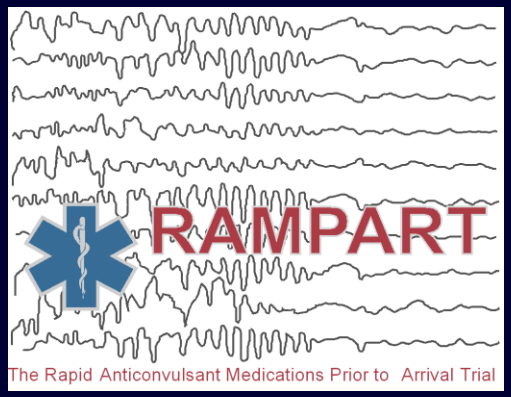


NETT

Rapid Anticonvulsant Medication Prior to Arrival Trial

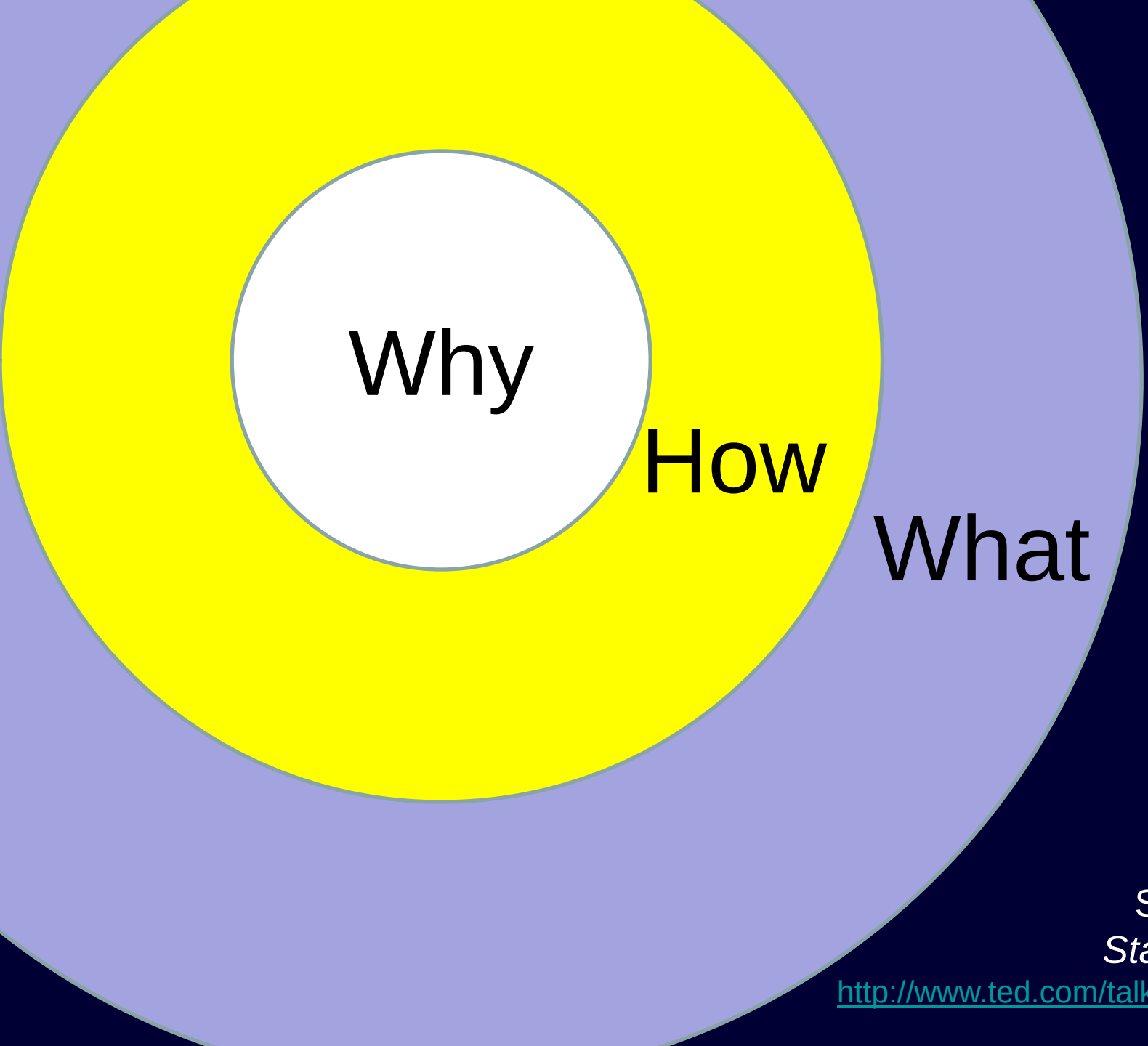
RAMPART

Supported by awards from the National Institute of Neurological Disorders and Stroke (NINDS) (U01NS056975 and U01NS059041); the National Institutes of Health Office of the Director CounterACT Program; and the Biomedical Advanced Research and Development Authority of the Assistant Secretary for Preparedness and Response.

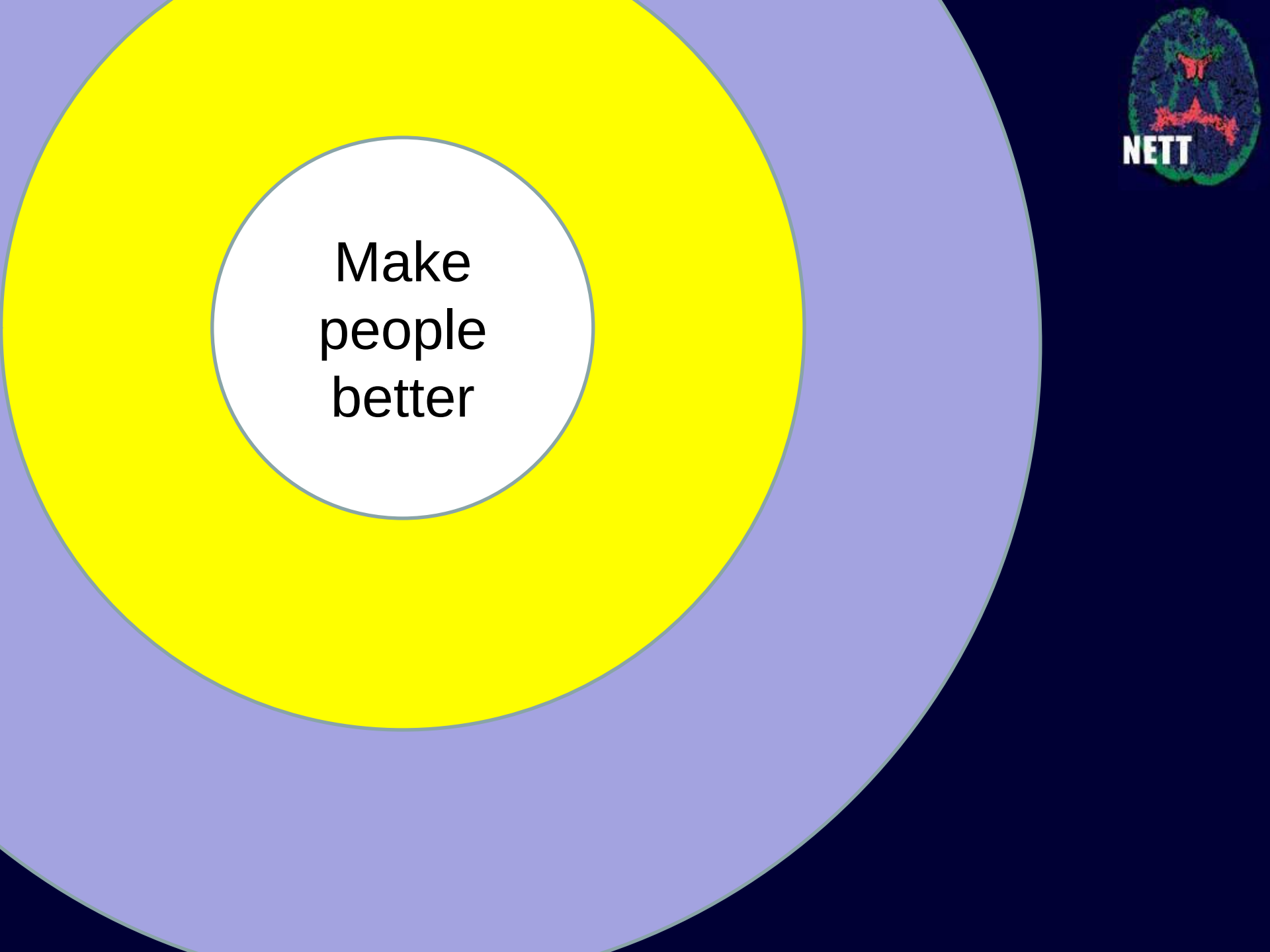
National Institute of Neurological Disorders and Stroke

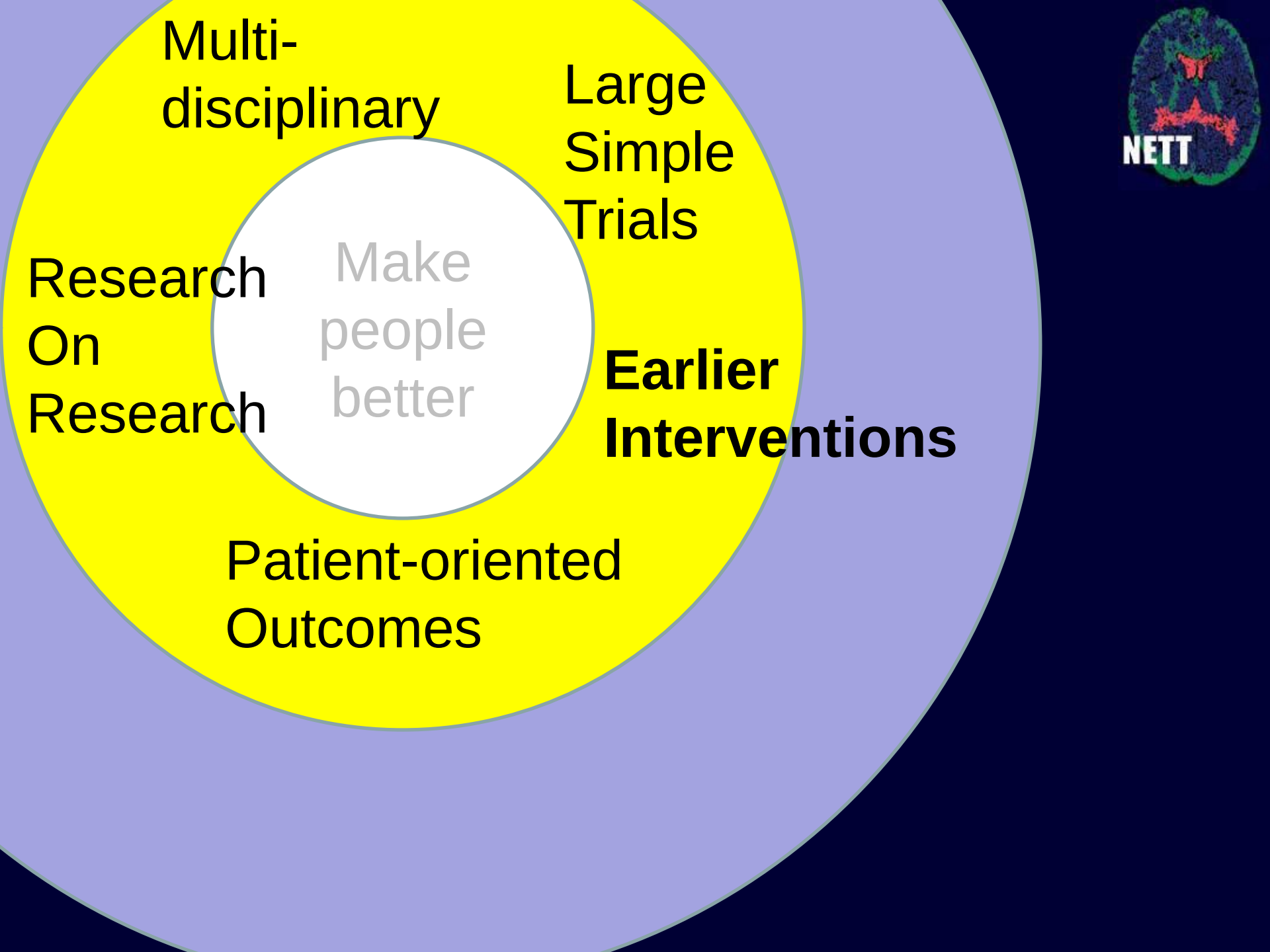
COUNTER ACT Countermeasures Against Chemical Threats

BARDA Biomedical Advanced Research and Development Authority



Simon Sinek
Start with Why
http://www.ted.com/talks/simon_sinek


Make
people
better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Make
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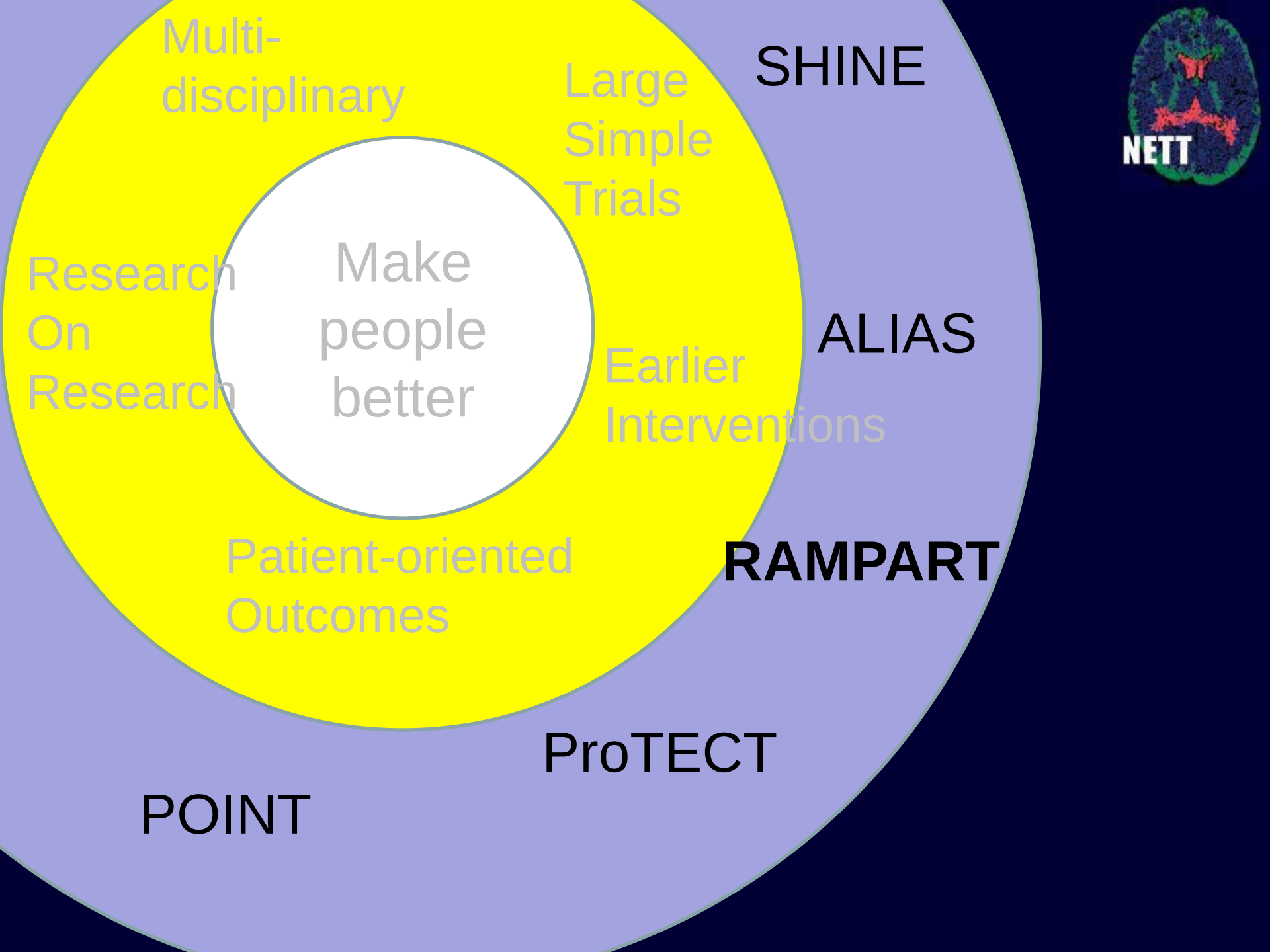
Earlier
Interventions
Patient-oriented
Outcomes
NETT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Outcomes
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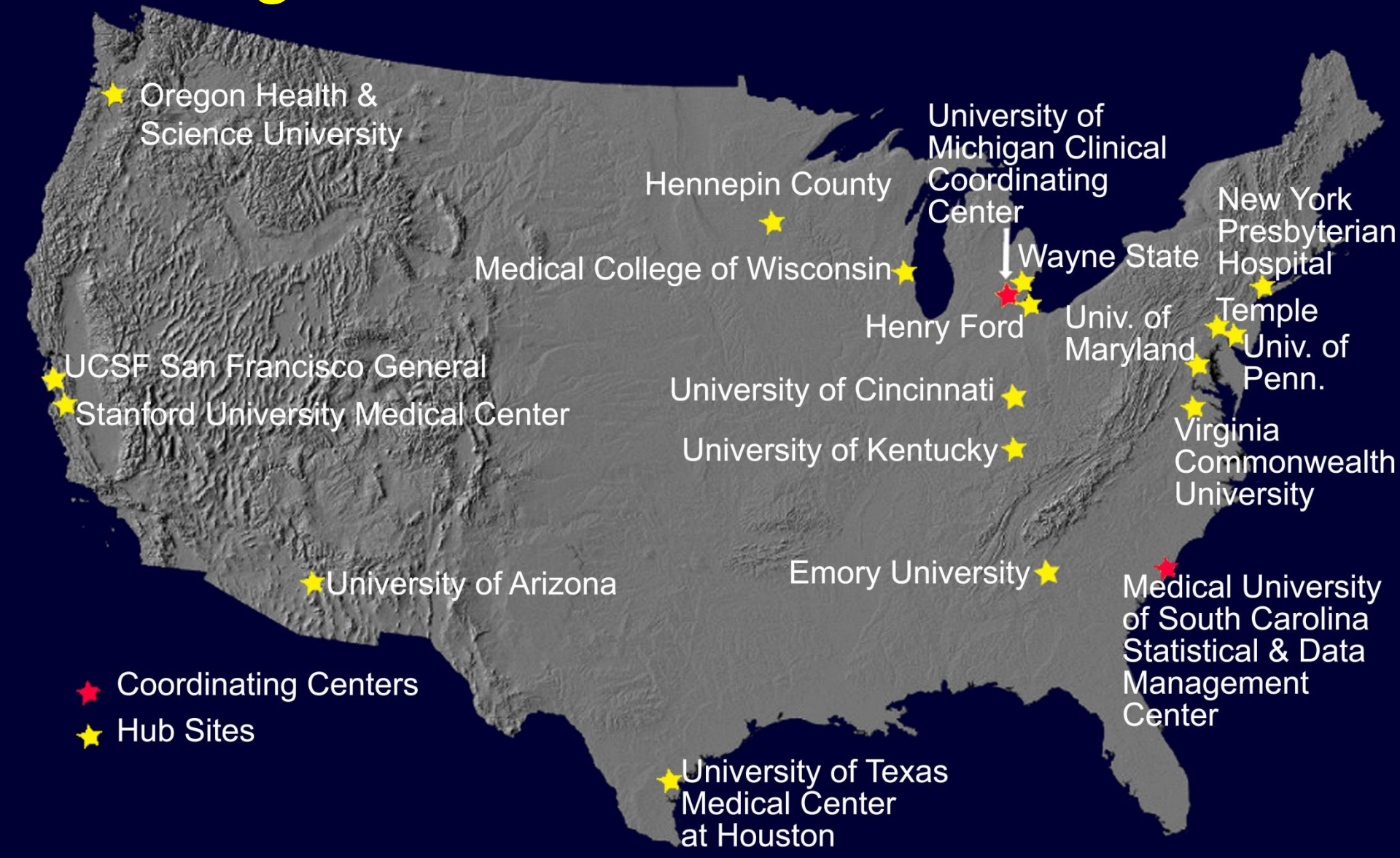
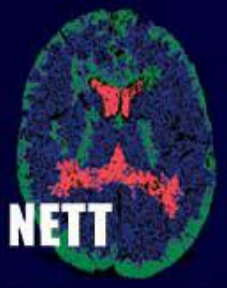
Background - NETT



Status Epilepticus



120,000 to 200,000 cases / yr

Mortality 22% at 30 days

55,000 deaths in the US

1st Yr cost $40,000 /patient

Bassin S, et al. Crit Care 2002;6(2):137-42

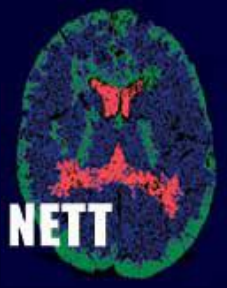
Claassen J, et al. Neurology 2002;58(1):139-42

DeLorenzo RJ, et al. Neurology 1996;46(4):1029-35

Penberthy LT, et al. Seizure 2005;14(1):46-51

Wu YW, et al. Neurology 2002;58(7):1070-6

San Francisco EMS Call Volume by Complaint Type (2001)



Chief Complaint	# Calls	(% of Total)	
Unconscious	7389	(11%)	
Falls / accidents	7224	(11%)	
Breathing difficulty	7225	(11%)	
Assault / trauma	6909	(10%)	
MVA	6098	(9%)	
Chest pain	5120	(8%)	
Seizure	4052	(6%)	> 10 per day
Abdominal pain	2593	(4%)	
Bleeding (non-traumatic)	1471	(2%)	
Stroke	1420	(2%)	

Pre-hospital Treatment of Status Epilepticus (PHTSE)

Alldredge et al. N Engl J Med 2001;345:631-7.

	LORAZEPAM (N=66)	DIAZEPAM (n=68)	PLACEBO (n=71)
	% of patients		
SE terminated prior to ED arrival	59.1	42.6	21.1

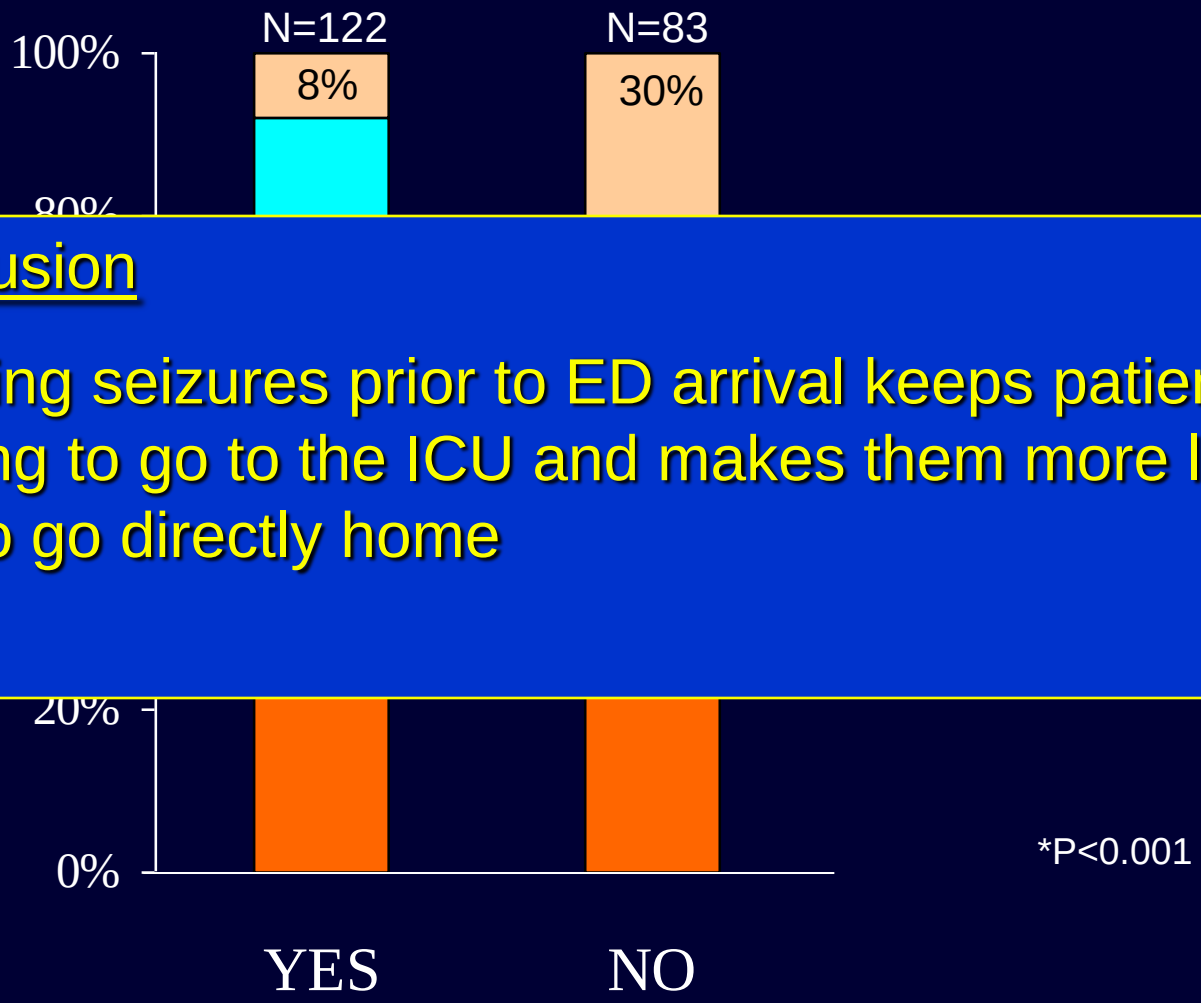
Conclusion

- Lorazepam and diazepam better than placebo
- Lorazepam probably better than diazepam

arrival, and cause of SE within prognostic group

Disposition of Patients from the Emergency Department

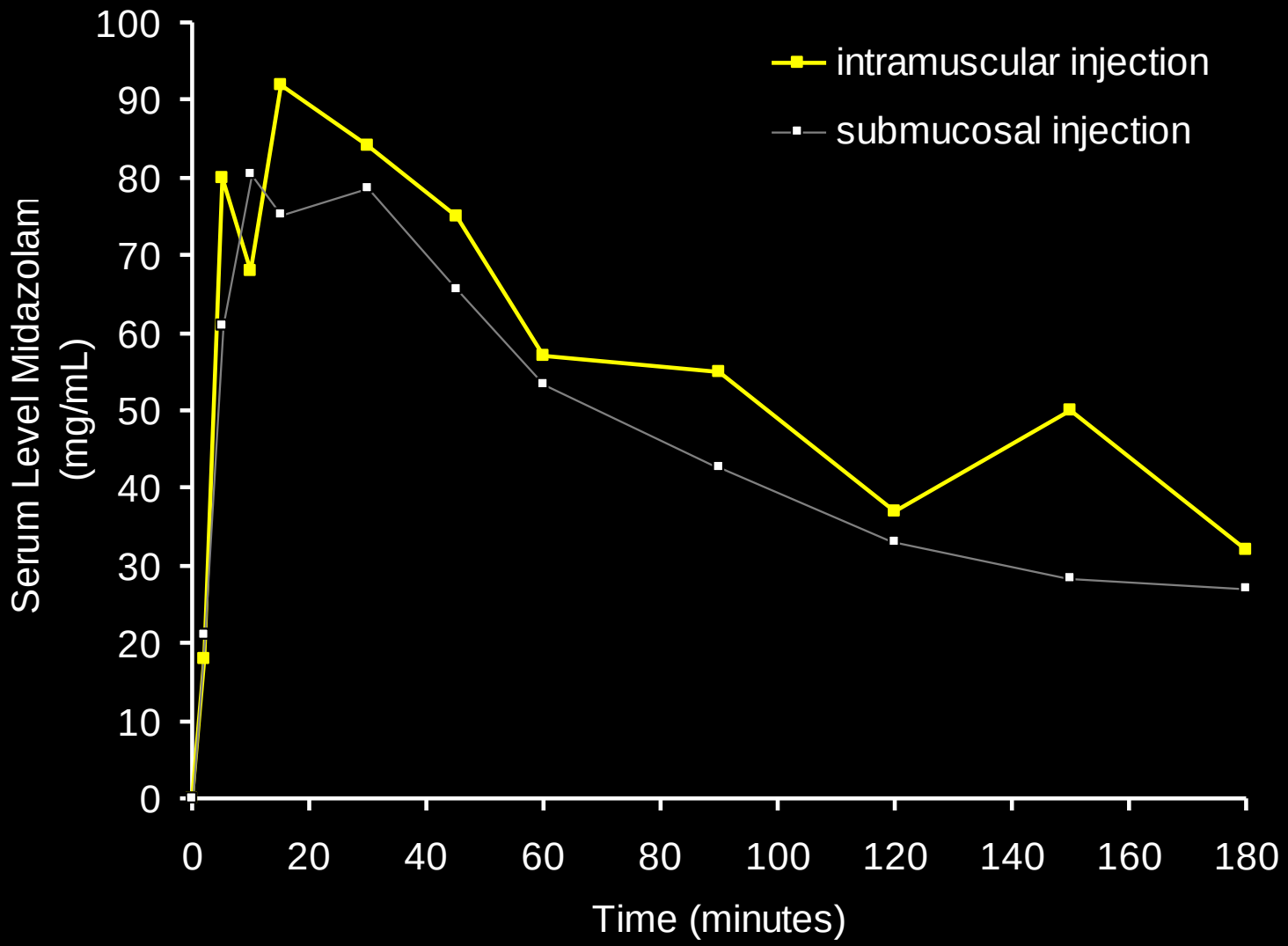
Alldredge et al. N Engl J Med 2001;345:631-7.



Conclusion

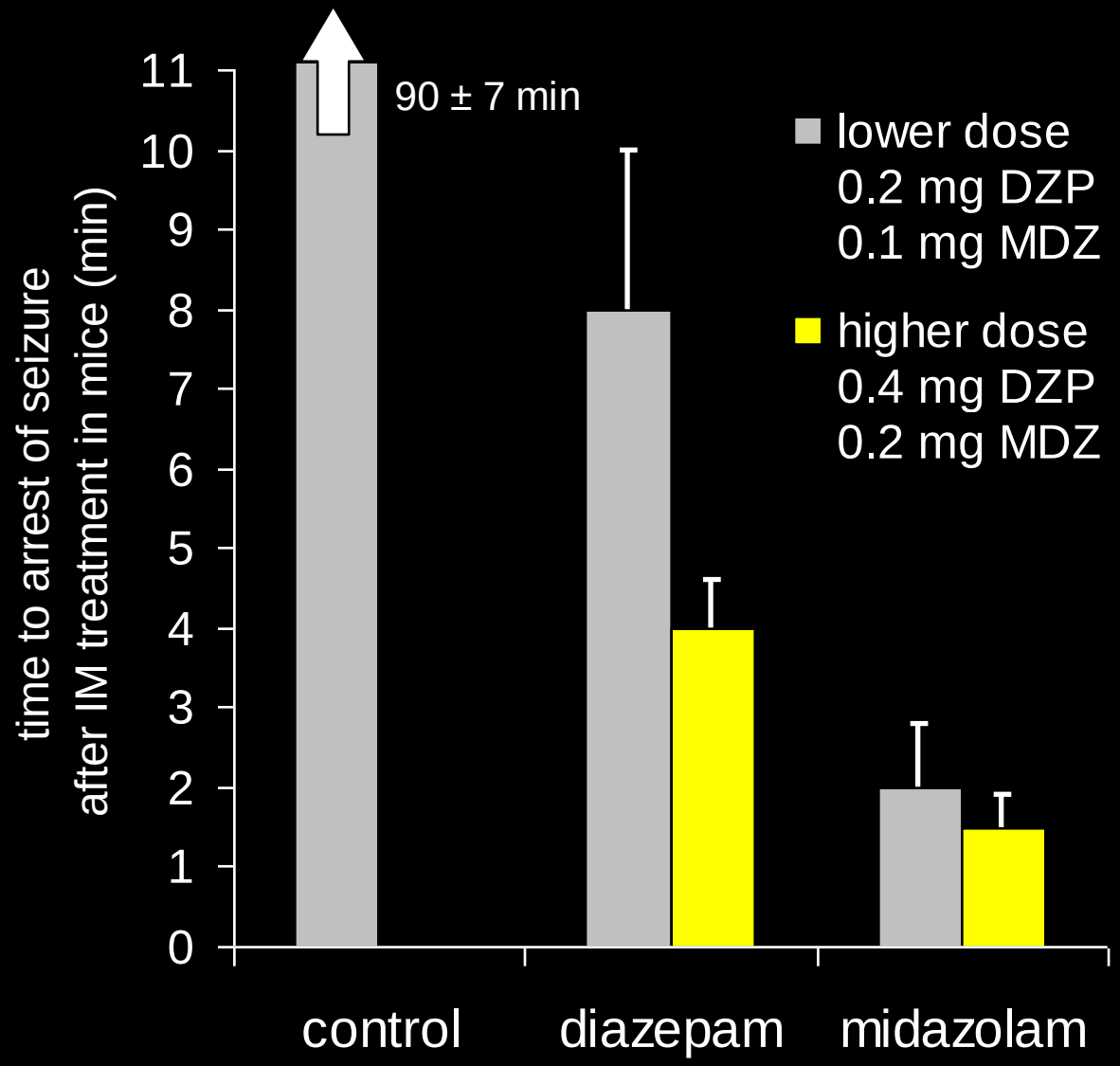
Stopping seizures prior to ED arrival keeps patients from needing to go to the ICU and makes them more likely to be able to go directly home

Midazolam levels near 80% of peak as early as 5 minutes after IM administration



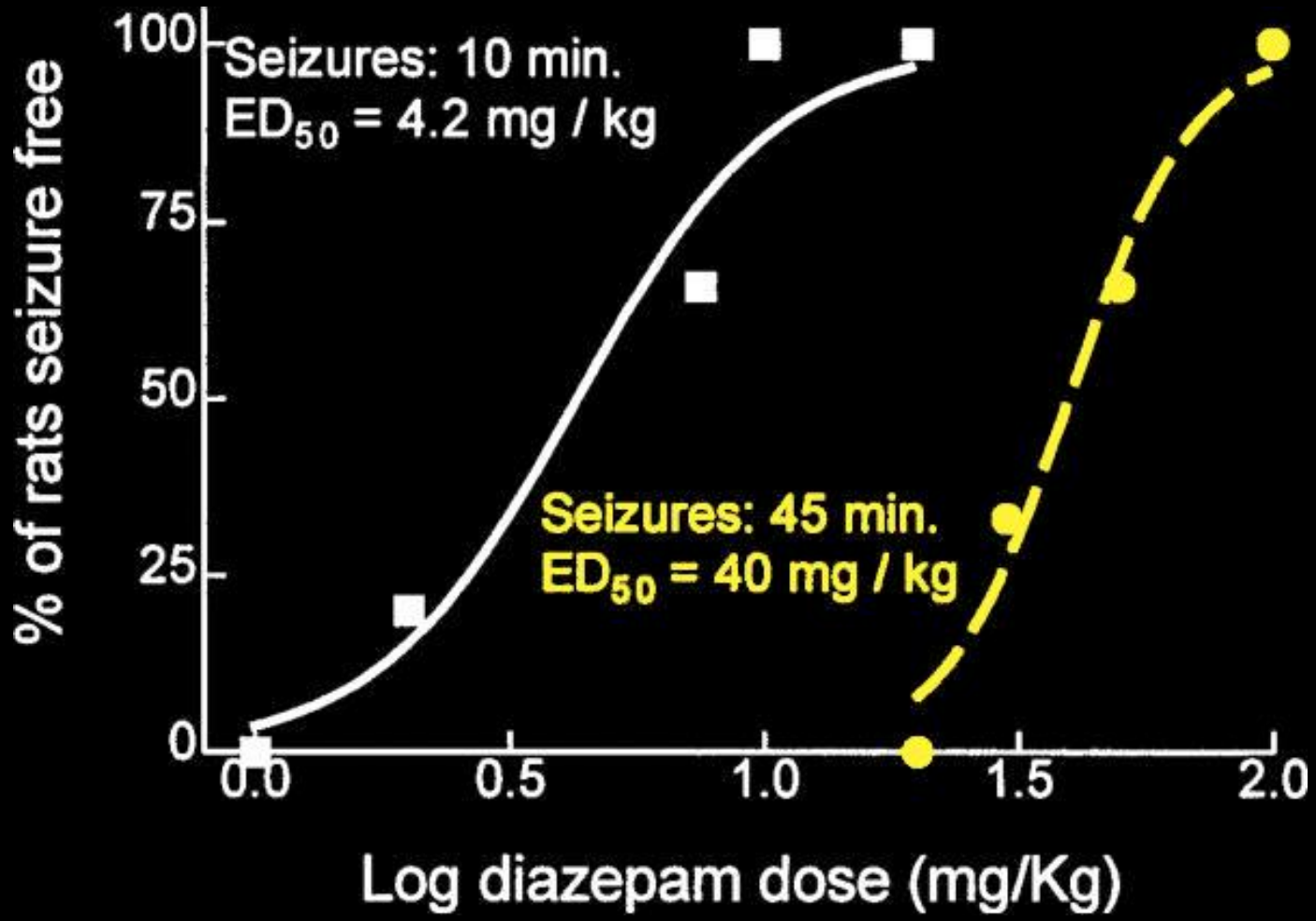
Alfonzo-Echeverri, Anesth Prog 1990;37:277-281

IM midazolam stops seizures 4 times faster than IM diazepam (in mice)



Raines, Epilepsia. 1990;31:313-7

Efficacy of benzodiazepines decreases with every minute of ongoing status epilepticus

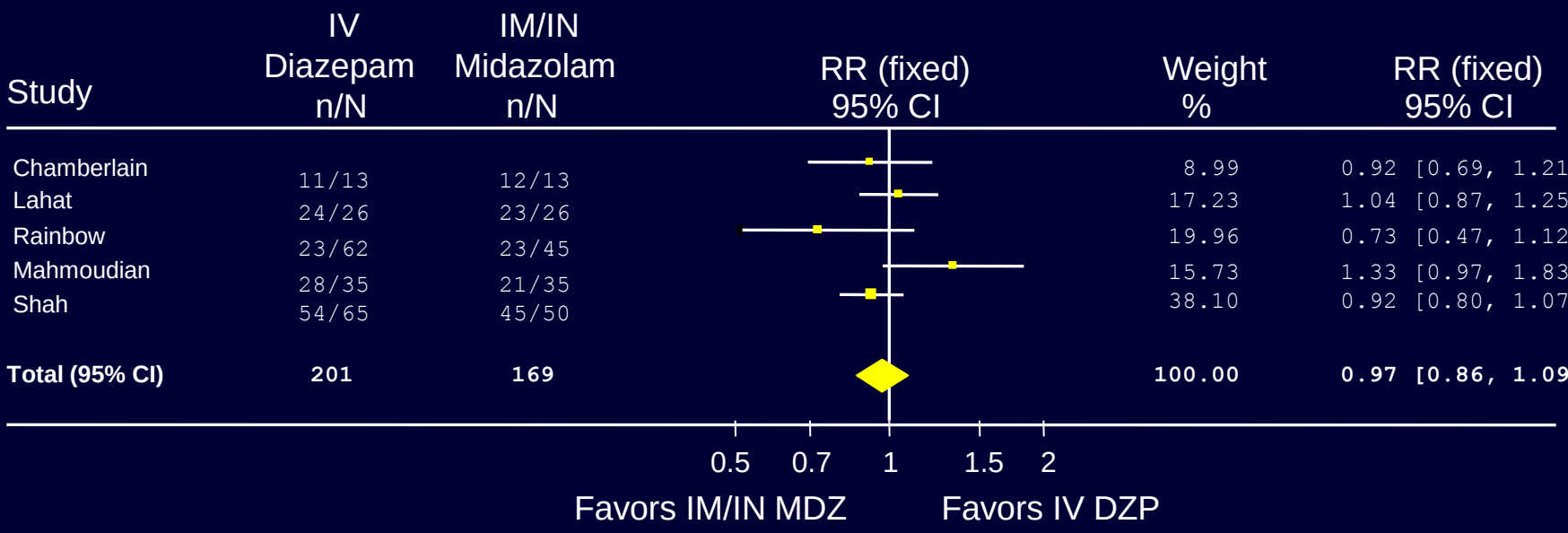


Kapur J, Macdonald RL. J Neurosci 1997;17(19):7532-40.

Meta-analysis of IM/IN midazolam shows the same efficacy as IV diazepam

Review: IV diazepam versus IM/IN midazolam for treatment of seizures
Comparison: 01 Effectiveness of IM/IN MDZ as compared to IV DZP

Outcome: 01 Termination of seizure

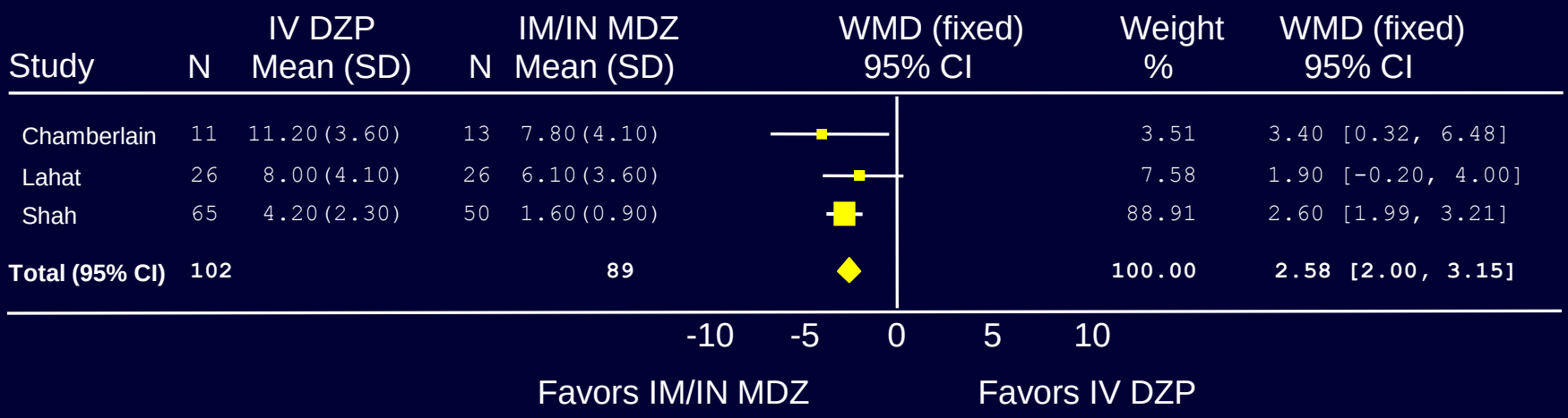


Total events: 140 (IV Diazepam), 124 (IM/IN Midazolam)
Test for heterogeneity: $Chi^2 = 6.87$, df = 4 (P = 0.14), $I^2 = 41.8\%$
Test for overall effect: Z = 0.54 (P = 0.59)

Meta-analysis of IM/IN midazolam shows more rapid termination of seizures compared to IV diazepam

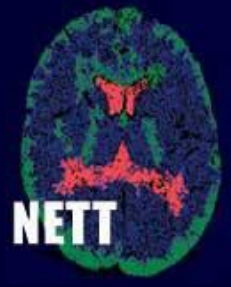
Review: IV diazepam versus IM/IN midazolam for treatment of seizures
Comparison: 01 Effectiveness of IM/IN MDZ as compared to IV DZP

Outcome: 02 Time to seizure control



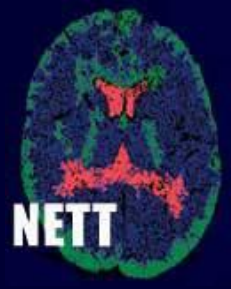
Test for heterogeneity: $Chi^2 = 0.68$, df = 2 ($P = 0.71$), $I^2 = 0\%$
Test for overall effect: $Z = 8.74$ ($P < 0.00001$)

Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) overview



- Paramedic treatment of status epilepticus
- Standard treatment is IV benzodiazepine
- IV starts difficult / dangerous in the convulsing patient
- Best IV agent, lorazepam, impractical for EMS
- IM treatment is faster and easier
- Best IM agent, midazolam, *is* practical for EMS

Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) overview



- IM midazolam autoinjector v. IV lorazepam
- Double dummy blinded design
- Exception to consent for emergency research
- Outcome: termination of seizure prior to ED arrival
- Sample 1024 enrollments (512 per group)
- Intention to treat, non-inferiority analysis

Aims

Primary Hypothesis

- IM midazolam is as effective as IV lorazepam at stopping convulsions prior to ED arrival

Secondary Hypotheses

- Convulsions stop more rapidly with treatment with IM midazolam versus IV lorazepam
- There is no difference in safety between the two treatments

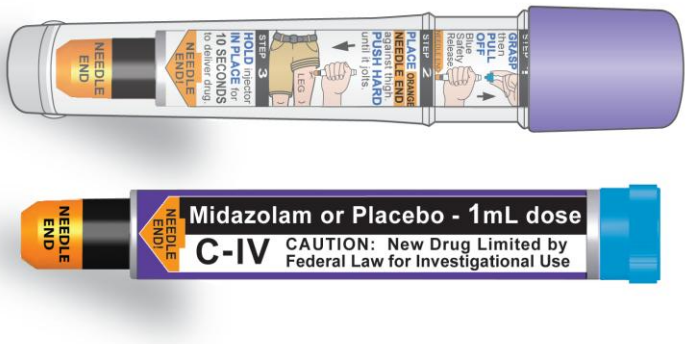
Inclusions

- Convulsive seizure activity for > 5 minutes
- Patient is still seizing
- Estimated weight > 13 kg

Exclusions

- Major trauma precipitating seizure
- Hypoglycemia
- Known allergy to midazolam or lorazepam
- Sensitivity to benzodiazepines
- Cardiac arrest or heart rate <40 beats/minute
- Known pregnancy
- Prisoner

Study Intervention

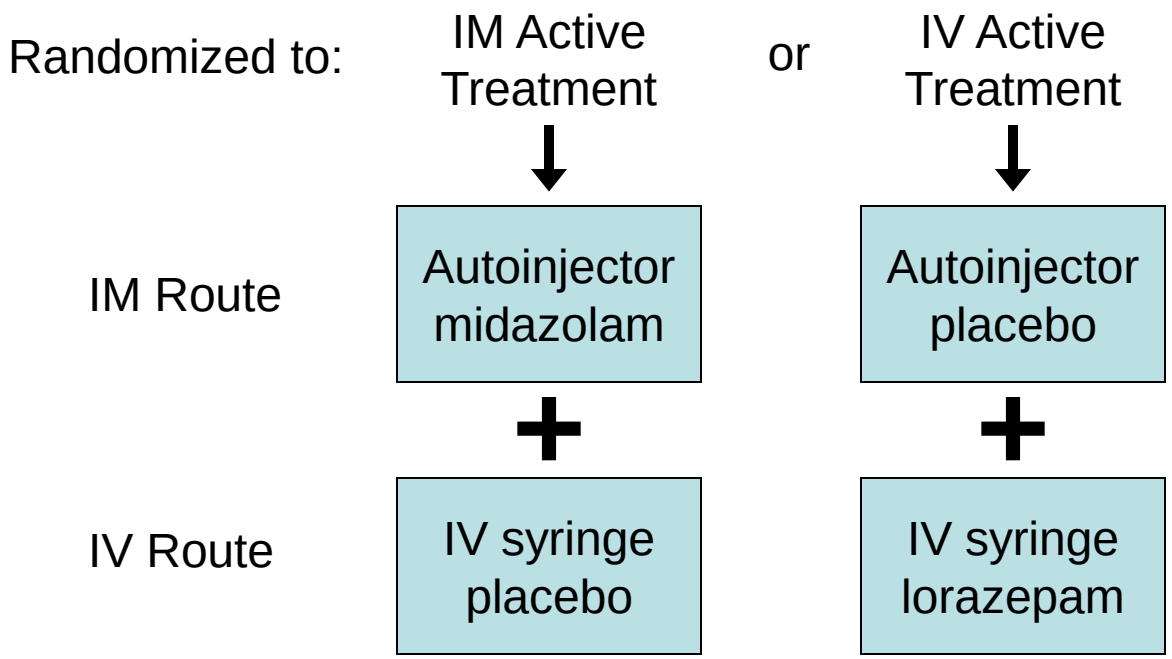


- Two packages in each box, Child dose and Adult dose
- Each package has one IM injector, one IV dose, one of which is active, the other is dummy

- Child (13- 39 kg) – Lorazepam 2 mg or Midazolam 5 mg
- Adult (40 kg and up)– Lorazepam 4 mg or Midazolam 10 mg

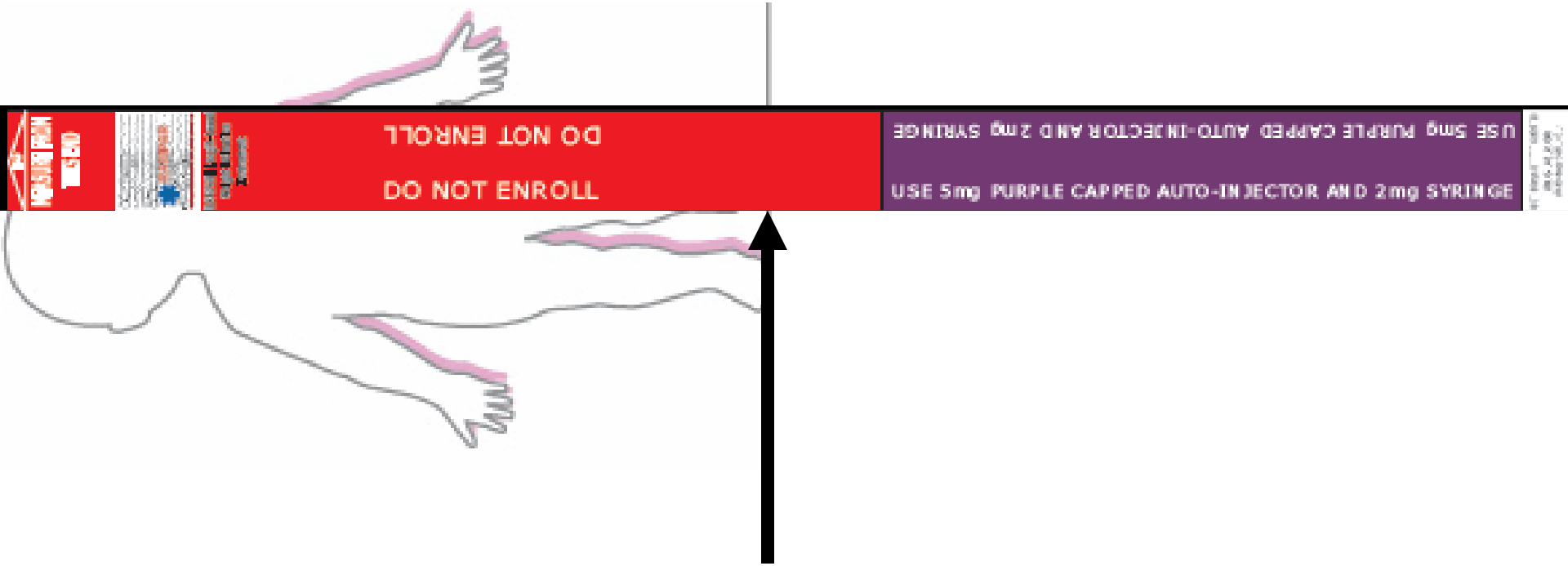
- Midazolam is in an autoinjector
- Lorazepam is given IV

Graphical representation of double-dummy design
All subjects get active treatment by either IM or IV route



Synopsis - Dose

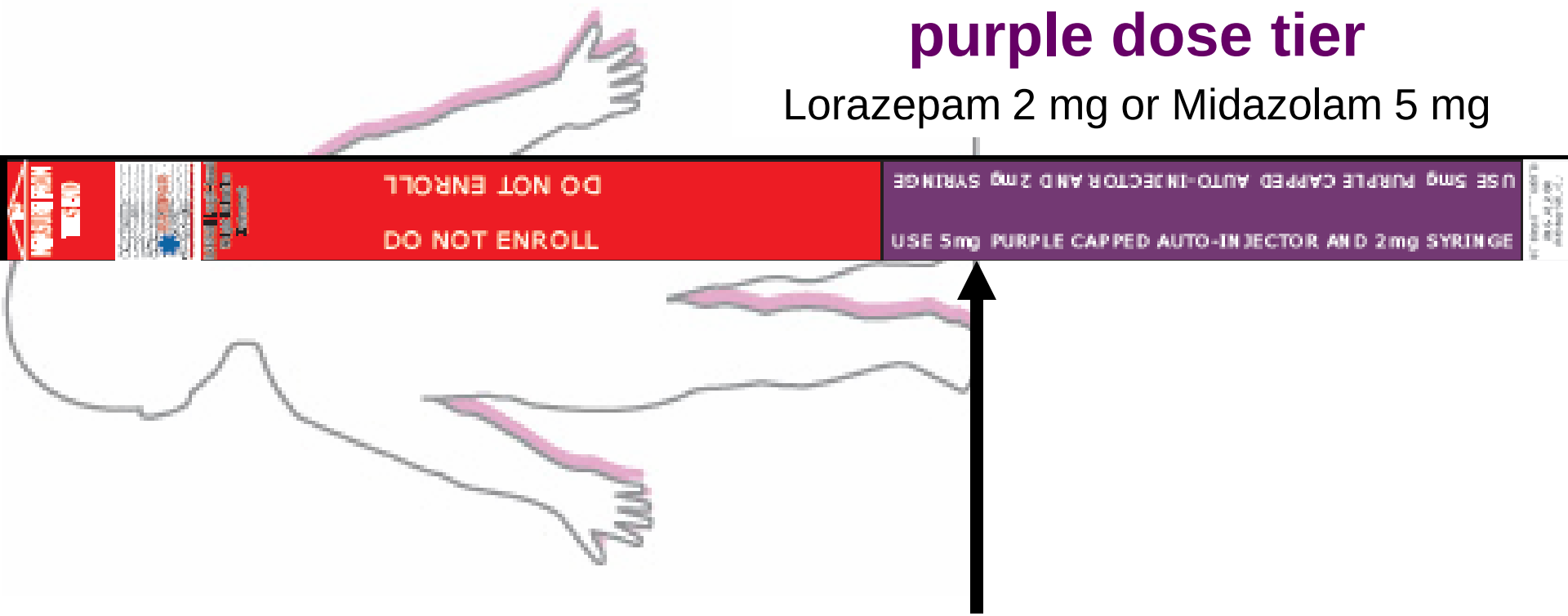
Infants and Children
Estimated < 13 kg
Are NOT enrolled



Synopsis - Dose

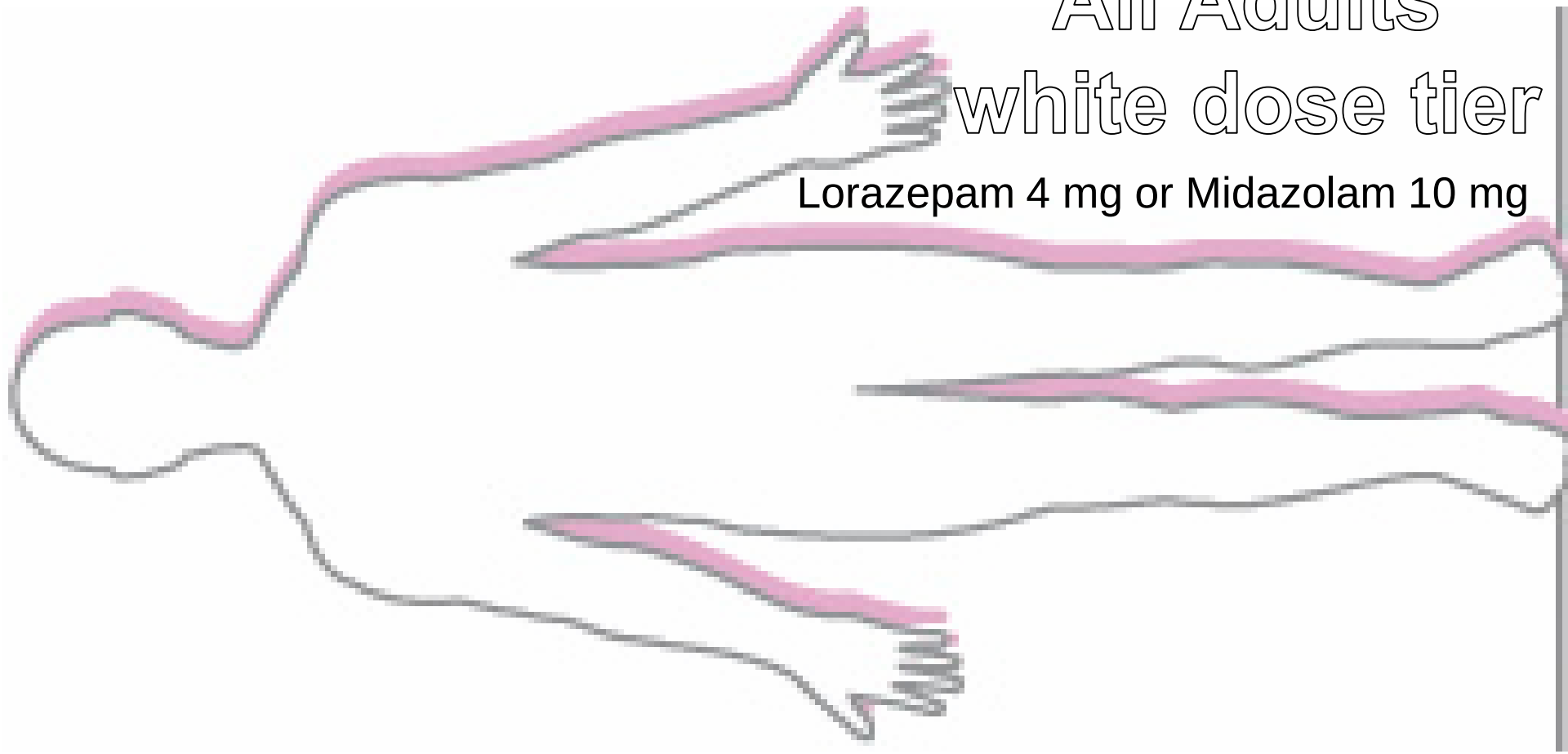
Children (13-39 kg) purple dose tier

Lorazepam 2 mg or Midazolam 5 mg

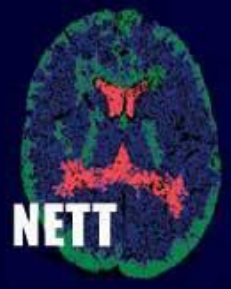


Synopsis - Dose

Synopsis - Dose



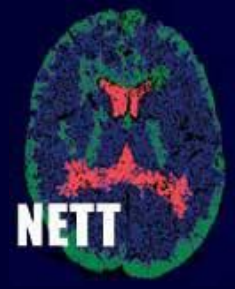
Primary outcome



- Proportion of subjects with termination of clinically evident seizure determined at arrival in the Emergency Department (ED) after a single dose of study medication.

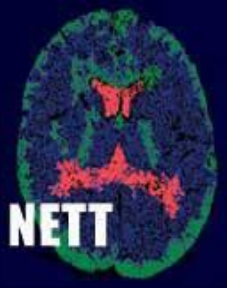
- Non-inferiority analysis designed to detect greater than 10% absolute difference in proportion with termination at ED arrival.

Secondary outcomes



- Rapidity of seizure termination
- Frequency of subsequent tracheal intubation
- Frequency and duration of ICU and hospital stay
- Frequency of seizure recurrence

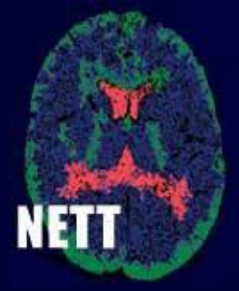
Sample Size



- Non-inferiority margin of 10%
- Power of 0.90
- Significance at 0.05
- Inflation for data loss and recidivists at 15%

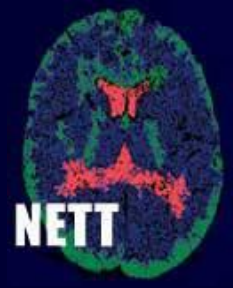
- N = 1024

Special Challenges



- Investigational New Drug application
- Exception from Informed Consent
- Time data collection in the field

Human subjects protection



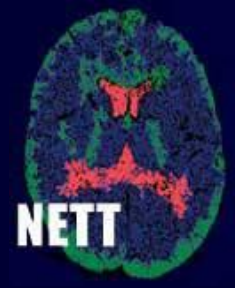
Benefits

- Both arms are accepted therapy
- Potential for direct benefit to subjects

Challenges

- Exception to Informed Consent
- IRB approval at all receiving hospitals

Exception to Informed Consent

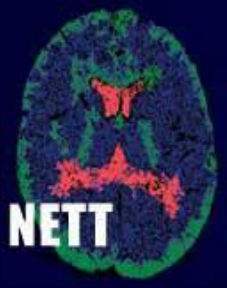


- Community Consultation
- Public Notification

- Local Context
- Centralized Support

- Local Outreach – attend community meetings
- Patient Focus Groups – survivors and clinics

EFIC, CC, and IRB process



- 225 community consultation activities at 17 hubs
- involving more than 23,898 participants
- >6,842 of whom provided direct feedback

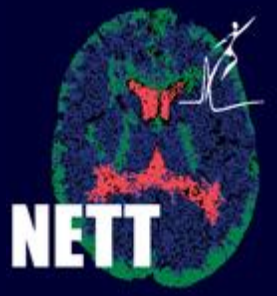
- IRB’s for 321 sites reviewed and approved


RAMPART
TEST v1.5

EMS training and deployment

- 4,314 medics trained
- 40 EMS Services in 14 States
  - Fire Service (67%)
  - Third Service or Hospital Based (33%)
- Wide ranging EMS system sizes
  - >100,000 runs/year (20%)
  - <5,000 runs/year (27%)
- Ambulances, Supervisor Units, Engines

Enrollment

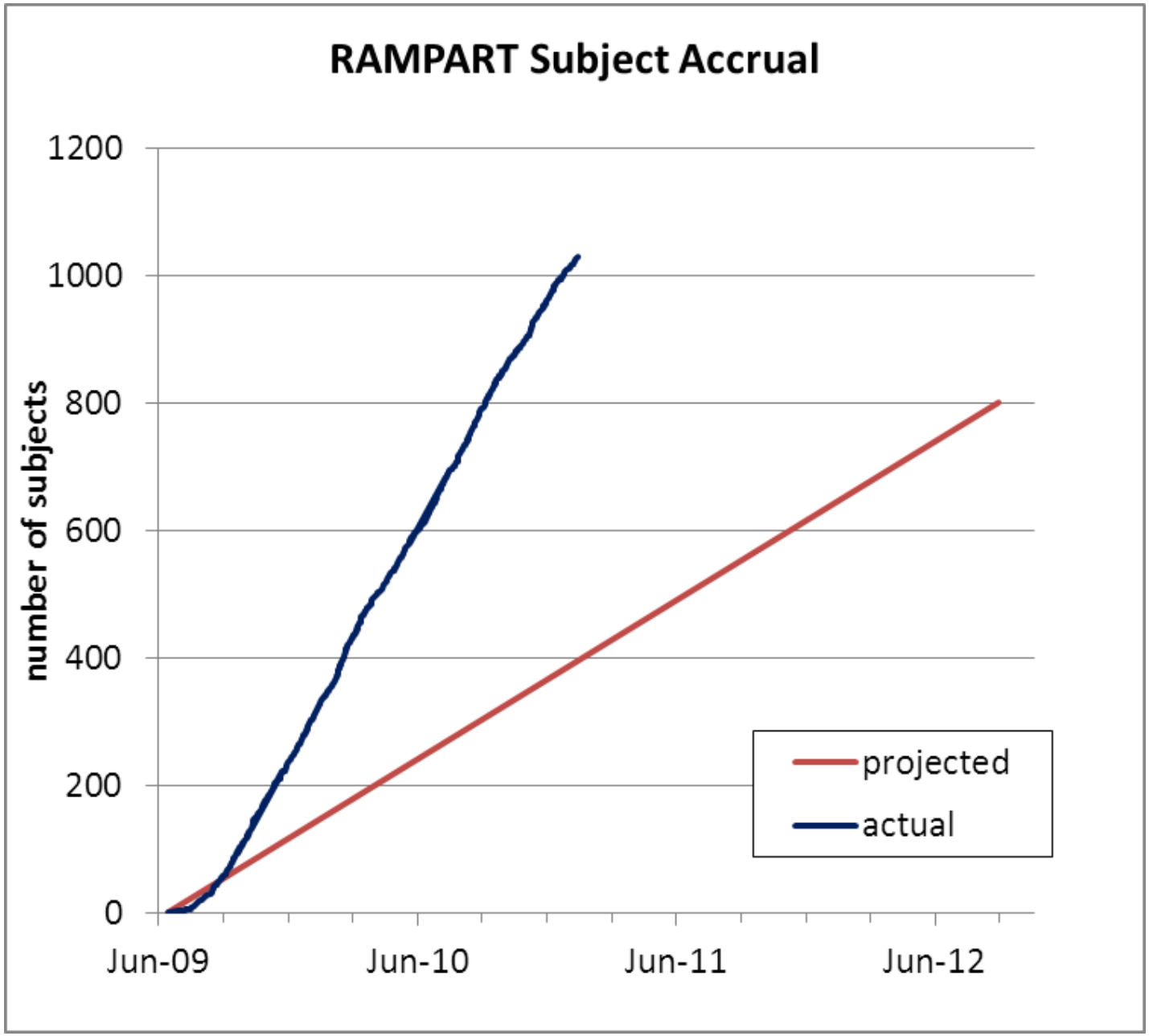


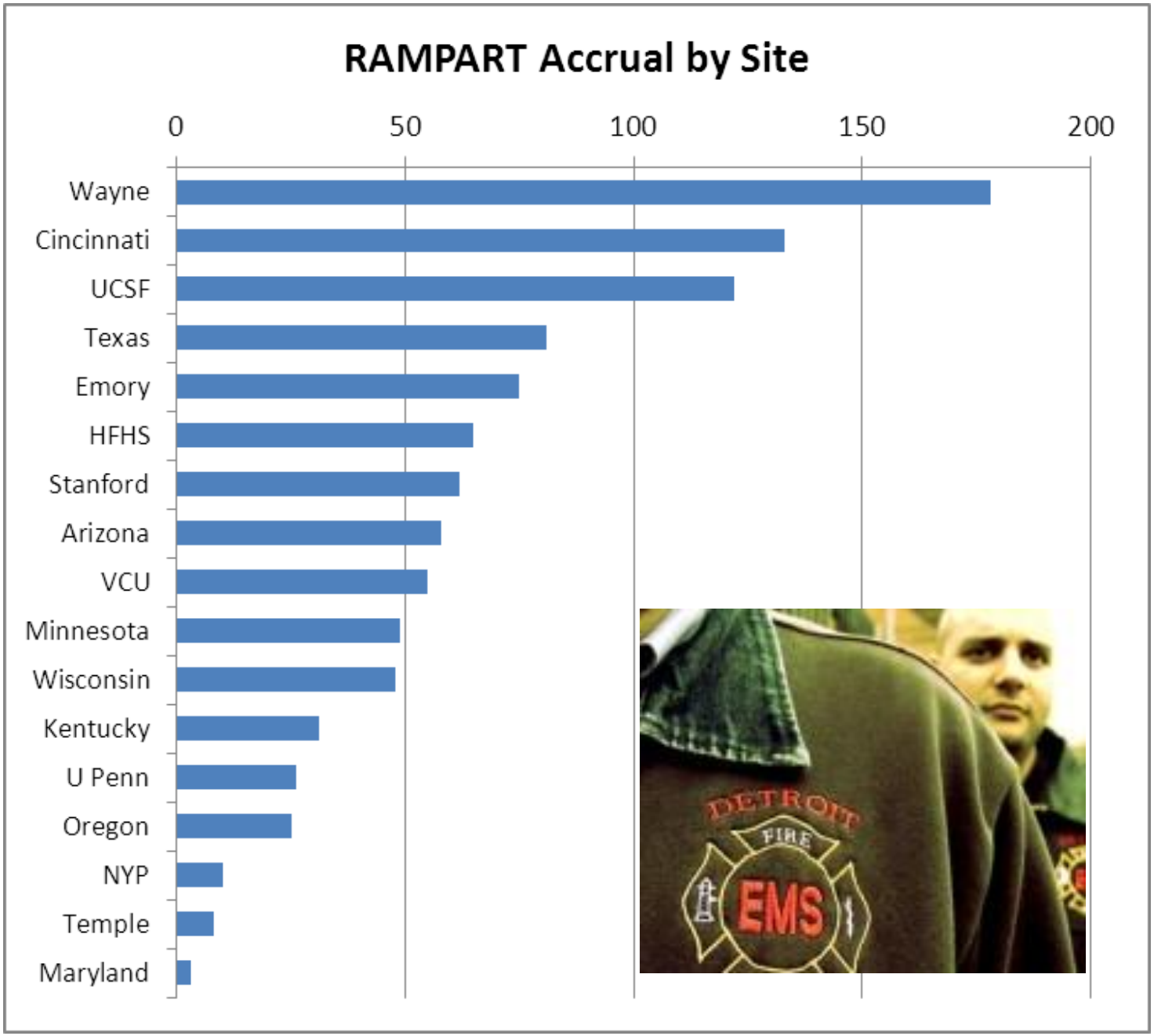
- 893 subjects were enrolled 1023 times
- Only the first enrollment of those enrolled more than once is included
- 732 in the Per Protocol (PP) population

Enrollment

- First subject in 6/15/2009

- Last subject in 1/14/2011


RAMPART Subject Accrual
number of subjects
1200
1000
800
600
400
200
0
Jun-09
Jun-10
Jun-11
Jun-12
projected
actual


RAMPART Accrual by Site
0
50
100
150
200
Wayne
Cincinnati
UCSF
Texas
Emory
HFHS
Stanford
Arizona
VCU
Minnesota
Wisconsin
Kentucky
U Penn
Oregon
NYP
Temple
Maryland
DETROIT
FIRE
EMS

Close-Out Performance

Last enrollment
1/14/2011

Last subject to reach end-of-study
4/10/2011

Database locked
4/22/2011

The NEW ENGLAND JOURNAL of MEDICINE

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Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

ABSTRACT

BACKGROUND

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the ces-

From the Department of Emergency Medicine, University of Michigan, Ann Arbor (R.S., W.B.); the Department of Medicine, Division of Biostatistics and Epidemiology, Medical University of South Carolina, Charleston (V.D., Y.P.); the Department of Neurology, University of California, San Francisco, San Francisco (D.L.); the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (R.C.); and the Department of Emergency Medicine, University of Cincinnati, Cincinnati (A.P.). Address reprint requests to Dr. Silbergleit at the Department of Emergency Medicine, Suite 3100, 24 Frank Lloyd Wright Dr., Ann Arbor, MI

Baseline Characteristics

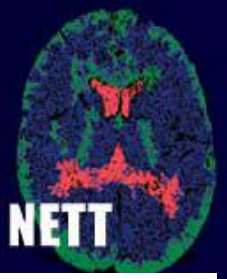


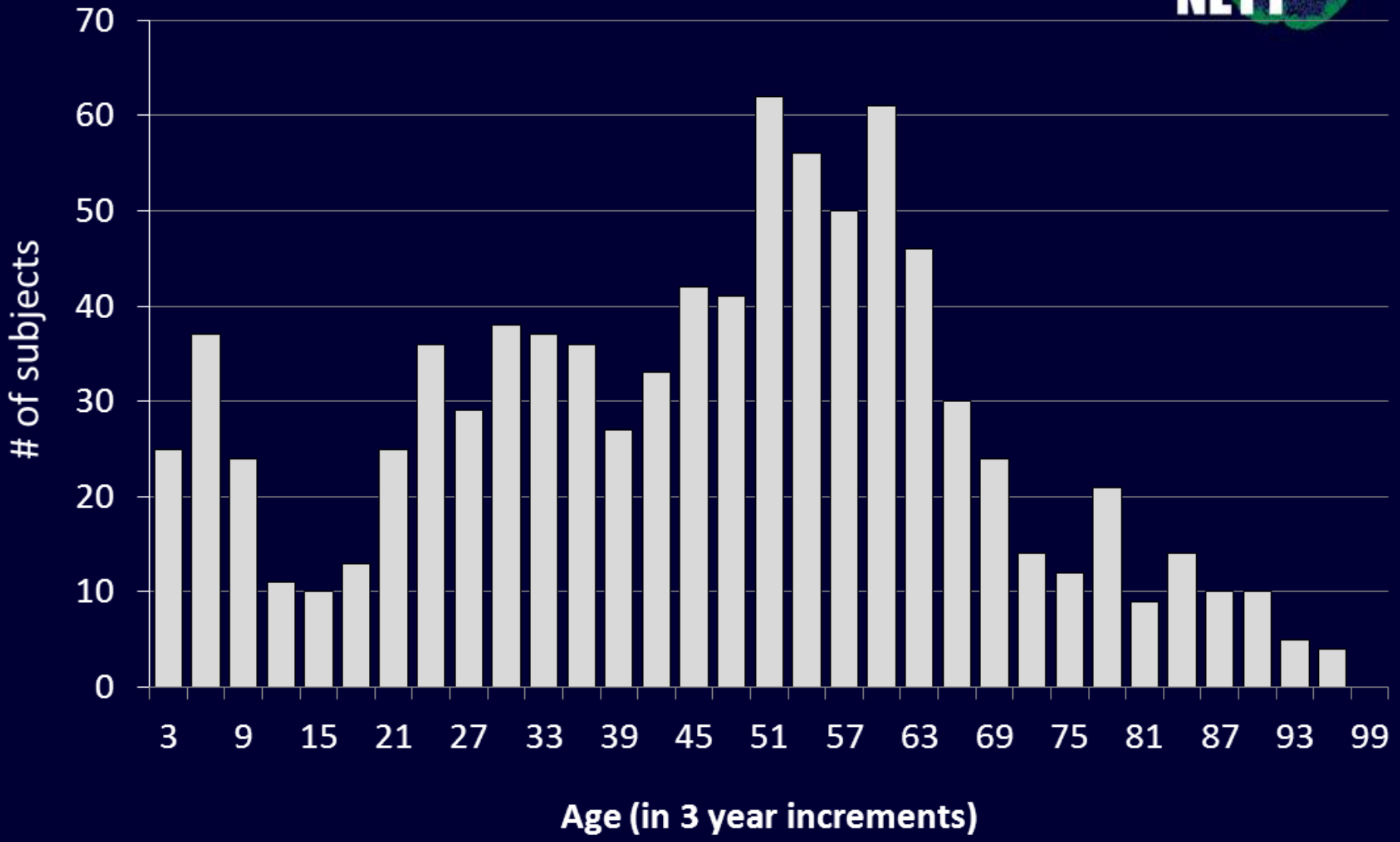
Table 1. Characteristics of the Subjects at Baseline.*

Characteristic	IM Midazolam (N=448)	IV Lorazepam (N=445)
Age		
Mean (range) — yr	43±22 (0–102)	44±22 (1–94)
Age group — no. (%)		
0–5 yr	32 (7)	29 (7)
6–10 yr	15 (3)	20 (4)
11–20 yr	28 (6)	21 (5)
21–40 yr	114 (25)	112 (25)
41–60 yr	169 (38)	169 (38)
≥61 yr	90 (20)	94 (21)
Male sex — no. (%)	250 (56)	238 (53)
Race — no. (%)†		
Black	229 (51)	224 (50)
White	165 (37)	183 (41)
Other, mixed, or unknown	54 (12)	38 (9)
Ethnic group — no. (%)†		
Non-Hispanic	310 (69)	290 (65)
Hispanic	49 (11)	57 (13)
Unknown	89 (20)	98 (22)

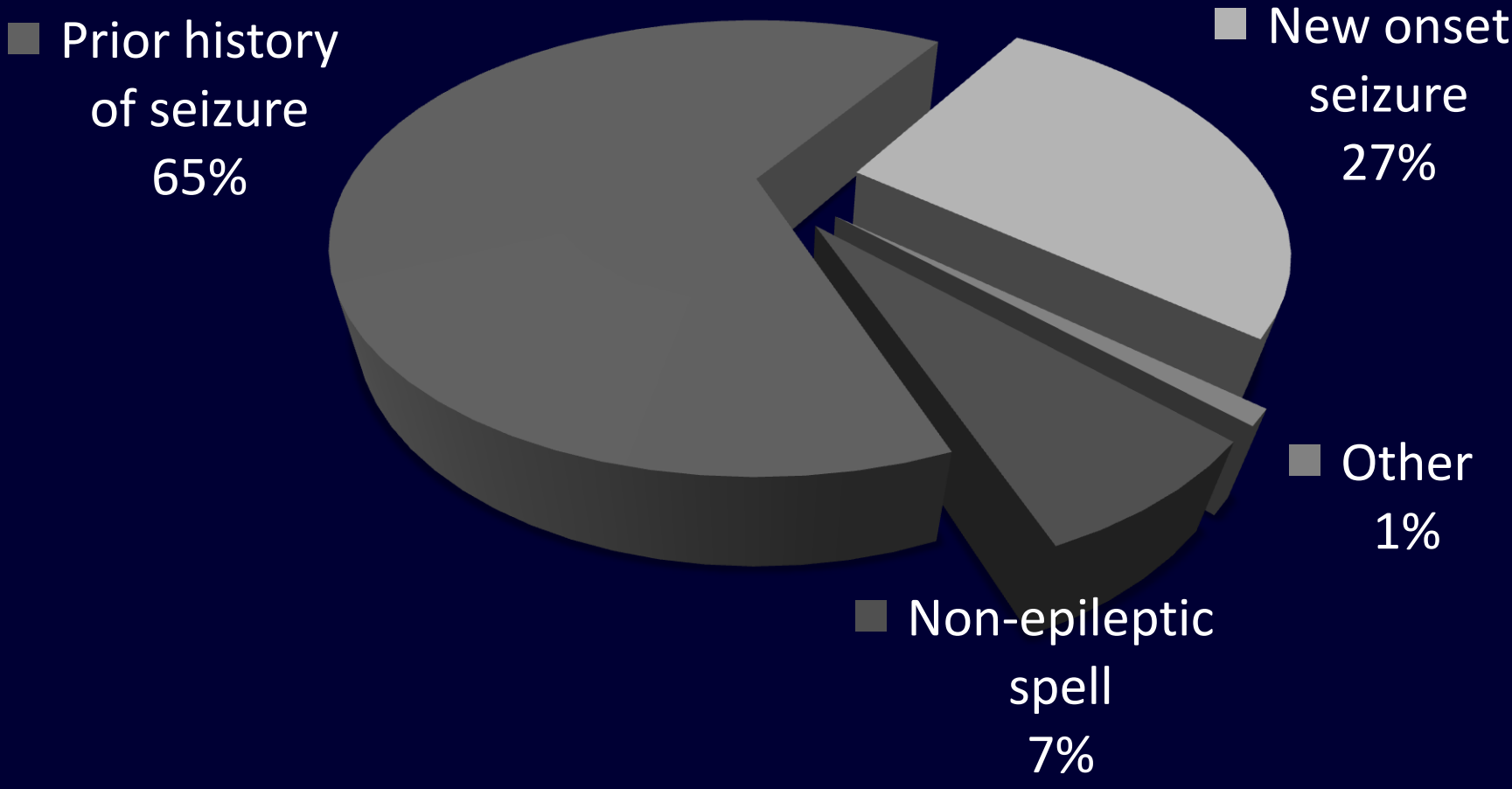
Table 1. Characteristics of the Subjects at Baseline.*

Characteristic	IM Midazolam (N=448)	IV Lorazepam (N=445)
Dose tier — no. (%)‡		
Low	62 (14)	59 (13)
High	386 (86)	386 (87)
History of epilepsy — no. (%)		
Yes	293 (65)	295 (66)
No	111 (25)	103 (23)
Not documented	44 (10)	47 (11)
Final diagnosis — no. (%)		
Status epilepticus	404 (90)	399 (90)
Nonepileptic spell	31 (7)	32 (7)
Undetermined	13 (3)	14 (3)
Precipitating cause of status epilepticus — no. (%)		
Noncompliance with or discontinuation of anticonvulsant therapy	137 (31)	141 (32)
Idiopathic or breakthrough status epilepticus	121 (27)	121 (27)
Coexisting condition that lowered seizure threshold	33 (7)	29 (7)

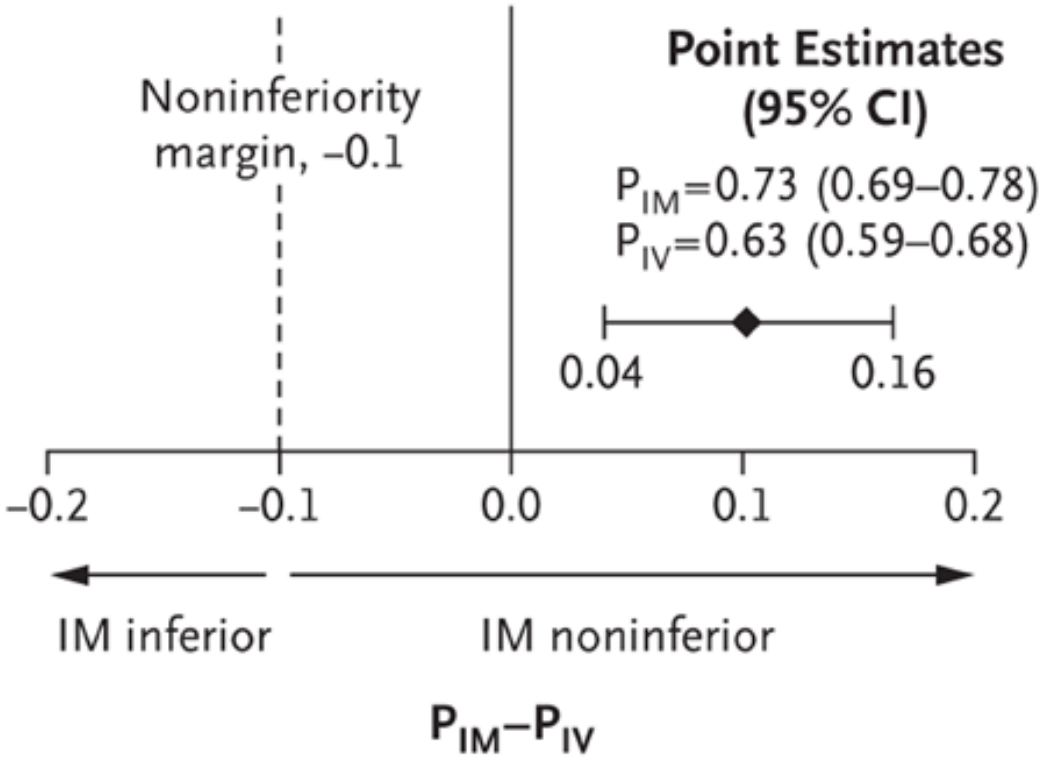
Demographics - Age



Etiology of SE in the study



Primary Outcome



Silbergleit R et al. N Engl J Med 2012;366:591-600

The NEW ENGLAND JOURNAL of MEDICINE

Primary Outcome

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Primary outcome				
Seizures terminated, no rescue therapy given				
No. of subjects	329	282	271	238
% of subjects (95% CI)§	73.4 (69.3–77.5)	63.4 (58.9–67.9)	74.9 (70.4–79.3)	64.3 (59.4–69.2)
Treatment failed — no. of subjects (%)	119 (26.6)	163 (36.6)	91 (25.1)	132 (35.7)
Seizures not terminated, no rescue therapy given	50 (11.2)	64 (14.4)	42 (11.6)	51 (13.8)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)	14 (3.9)	38 (10.3)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)	35 (9.7)	43 (11.6)

Silbergleit R et al. N Engl J Med 2012;366:591-600

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Secondary Outcomes

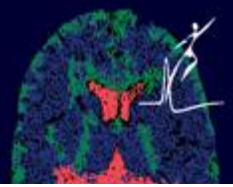
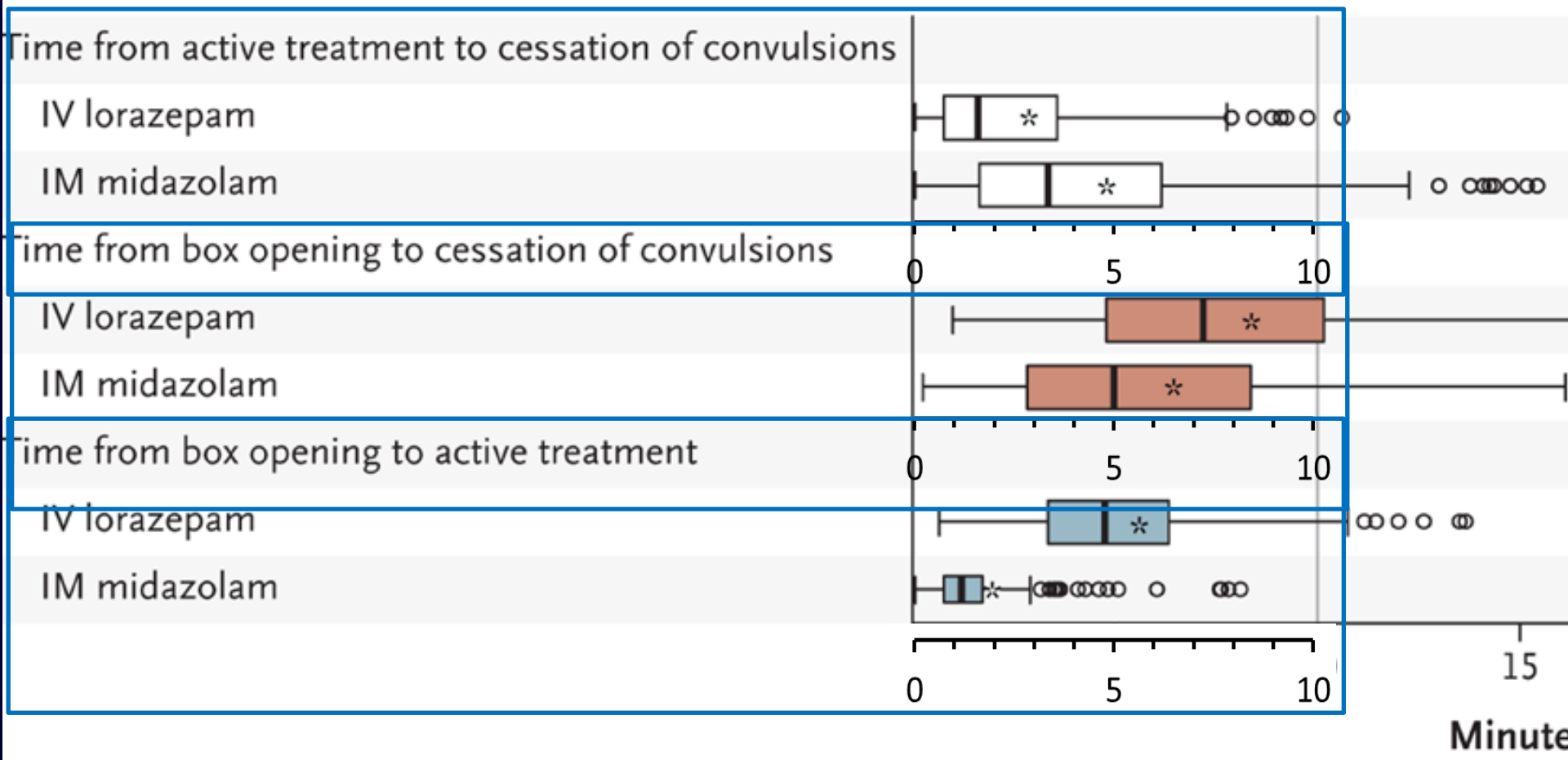


Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Secondary outcomes				
Endotracheal intubation within 30 min after ED arrival				
No. of subjects — %	63 (14.1)	64 (14.4)	53 (14.6)	53 (14.3)
Relative risk (95% CI)	0.98 (0.70–1.34)		1.02 (0.71–1.45)	
Hospitalization				
No. of subjects — %	258 (57.6)	292 (65.6)	210 (58.0)	250 (67.6)
Relative risk (95% CI)	0.88 (0.79–0.98)		0.86 (0.77–0.96)	
ICU admission				
No. of subjects — %	128 (28.6)	161 (36.2)	102 (28.2)	138 (37.3)
Relative risk (95% CI)	0.79 (0.65–0.95)		0.76 (0.61–0.93)	
Recurrent seizure within 12 hr after ED arrival				
No. of subjects — %	51 (11.4)	47 (10.6)	37 (10.2)	39 (10.5)
Relative risk (95% CI)	1.08 (0.74–1.56)		0.97 (0.63–1.48)	
Hypotension				
No. of subjects — %	12 (2.7)	13 (2.9)	5 (1.4)	9 (2.4)
Relative risk (95% CI)	0.92 (0.42–1.98)		0.57 (0.19–1.67)	

Time Outcomes



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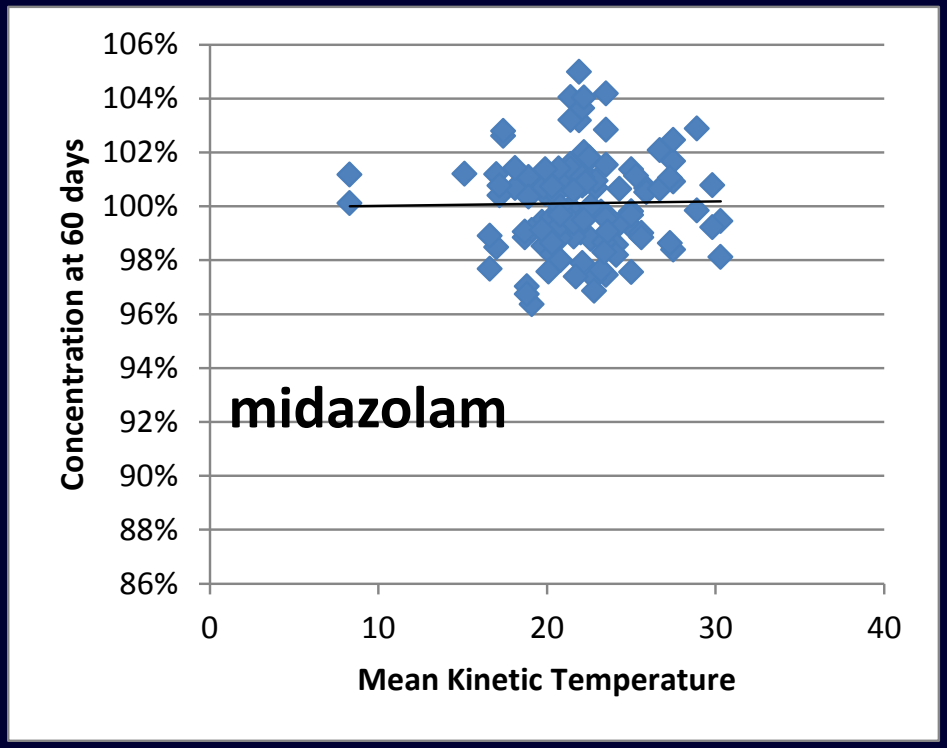
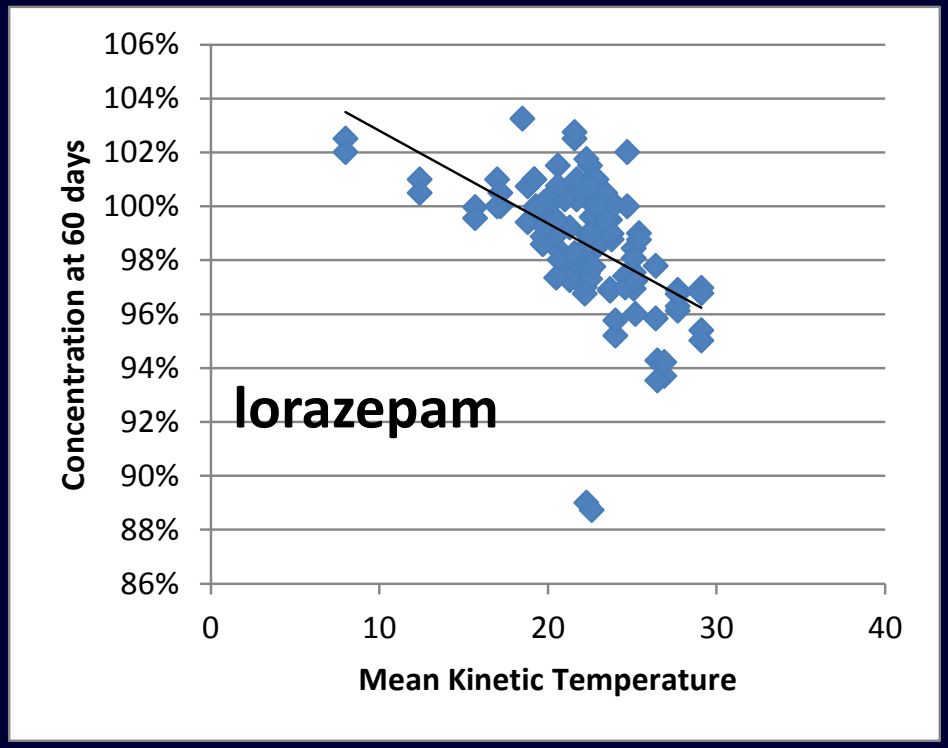
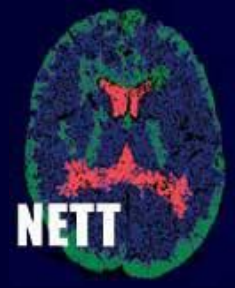
In-field stability and temperature





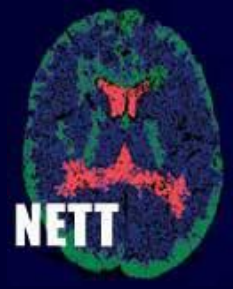
Summary – accompanying editorial



"…the findings in this study should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital."

Lawrence Hirsch

Summary



- Intramuscular midazolam is the optimal initial prehospital treatment for status epilepticus by paramedics
- Next steps are facilitating clinical (T2) translation
- Focus on the next step… what is the optimal second line agent in the ED for those with status epilepticus refractory to benzodiazepines?

Acknowledgements

NETT CCC
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Robin Conwit
Scott Janis
Brandy Fureman
David Jett

NETT SDMC
Valerie Durkalski
Yuko Palesch
Wenle Zhao
Catherine Dillon
Angela Wu

Our subjects &
Thousands of medics

DSMB
Tom Bleck
Gail Anderson
Jim Chamberlain
Joseph Collins
Peter Gilbert
Jeff Saver

Hub PI's
Tom Aufderheide
Jill Baren
Michelle Biros
Kurt Denninghoff
Nina Gentile
J. Claude Hemphill III
Roger Humphries
Elizabeth Jones
Christopher Lewandowski
Robert Lowe
Stephan Mayer
Joseph P. Ornato
Arthur Pancioli
James V. Quinn
Barney J. Stern
Robert Welch
David Wright




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PARAMEDIC

FRIED CHICKEN
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BALTIMORE CITY
FIRE DEPARTMENT


EMERGENCY MEDICAL SERVICES
CMC
Level I Trauma Center
PARAMEDIC

NewYork-Presbyterian
EMERGENCY MEDICAL SERVICES

EMS

M 89
S.F.
M 67
S.F.F.D.

LEXINGTON
FIRE DEPARTMENT
EMERGENCY MEDICAL SERVICES
6

71
EMERGENCY MEDICAL SERVICES
RICHMOND AMBULANCE AUTHORITY

SAN MATEO
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FULTON COUNTY EMS
Grady Health System
Emergency Medical Service
ADVANCED LIFE SUPPORT
25B


NETT
Neurological Emergencies Treatment Trials
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WAYNE STATE UNIVERSITY
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EMORY
UNIVERSITY

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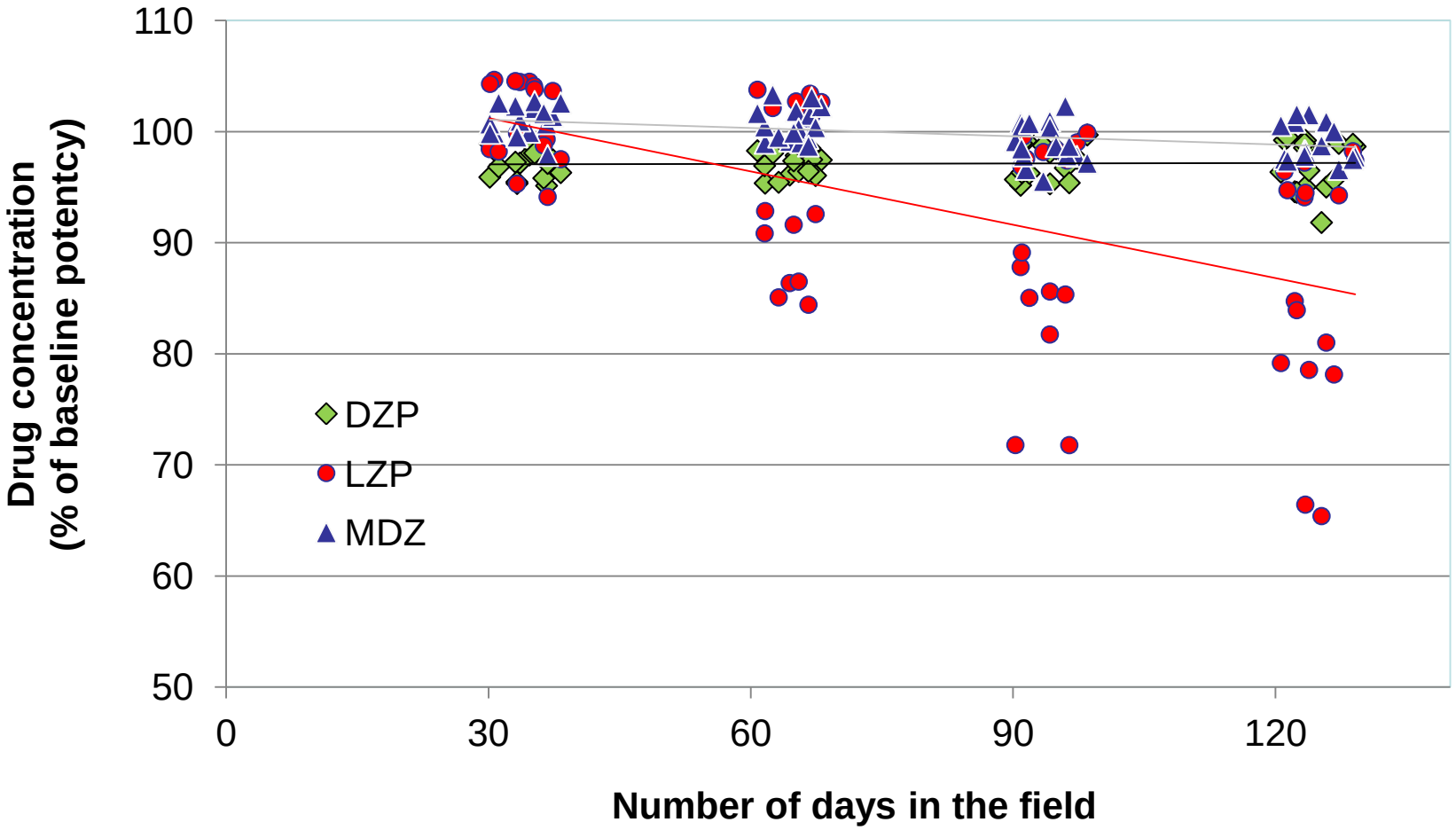
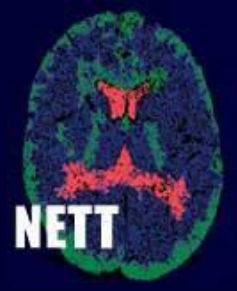
nett.umich.edu

Loss of lorazepam potency with time in the field



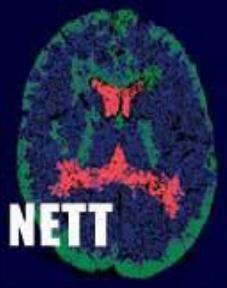
Prehospital Intubations



- PHTSE (supported respirations BVM / intubation)
  - IV LZP 7/66 11%
  - IV DZP 6/68 9%
  - IV Placebo 11/71 15%

- RAMPART (completed / attempted advanced airway)
  - IV LZP 7/509 1%
  - IM MDZ 13/514 3%

Persistent seizures and intubation

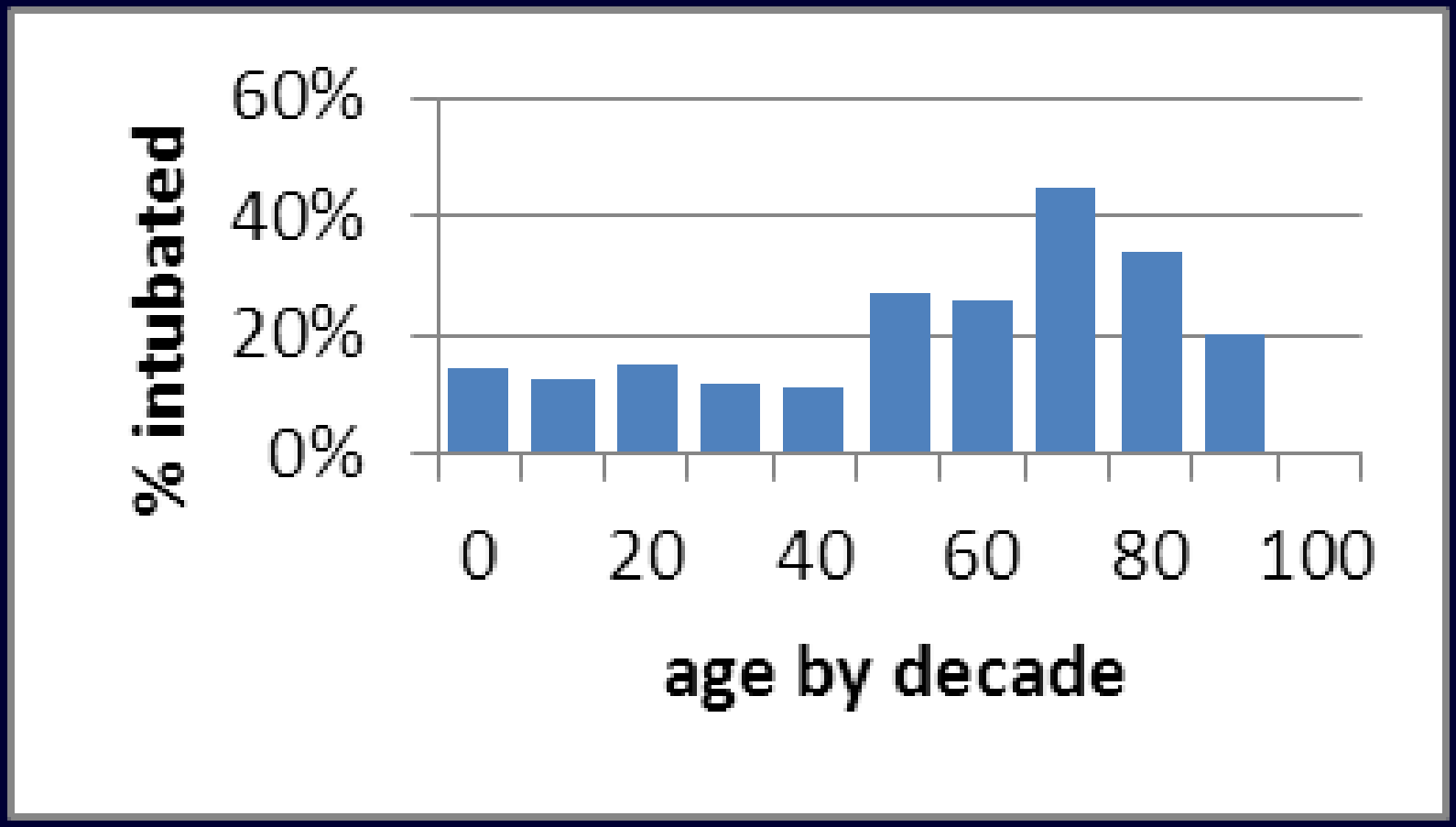


- Primary outcome predicts intubation (enrollments)
  - Treatment success 105/691 15%
  - Treatment failures 95/33 29%

- About 1/3 enrollments were seizing at the time of intubation

- Most had additional benzodiazepines in the ED prior to the decision to intubate

Most intubations in older adults



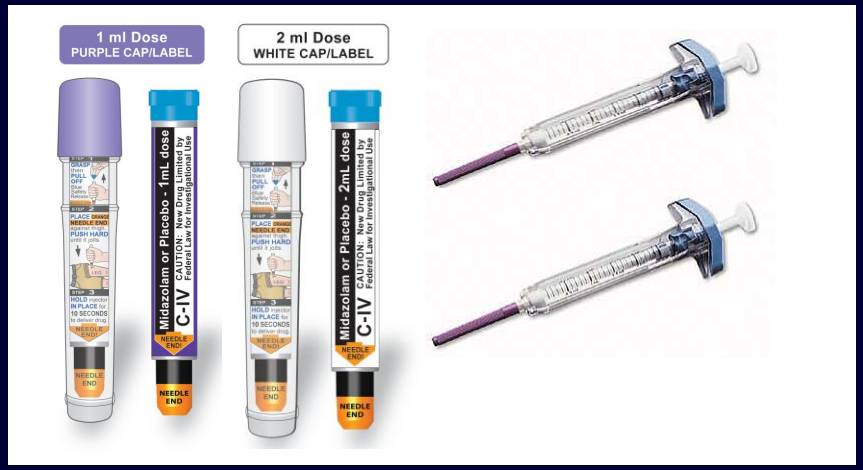
IV not administered

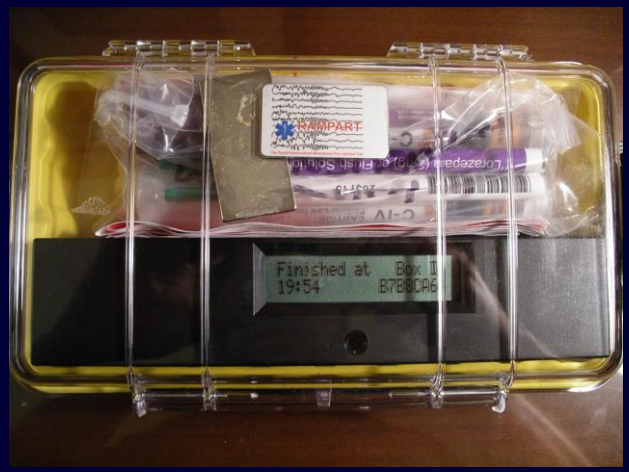
		IM midazolam (N=448)		IV lorazepam (N=445)	
IV not administered	n(% of total ITT)	216	(48%)	148	(33%)
Reason	n(% of total ITT)				
Seizure stopped before IV could be started		174	(39%)	95	(21%)
Medics unable to start IV before ED arrival		27	(6%)	42	(9%)
Other		15	(3%)	11	(2%)

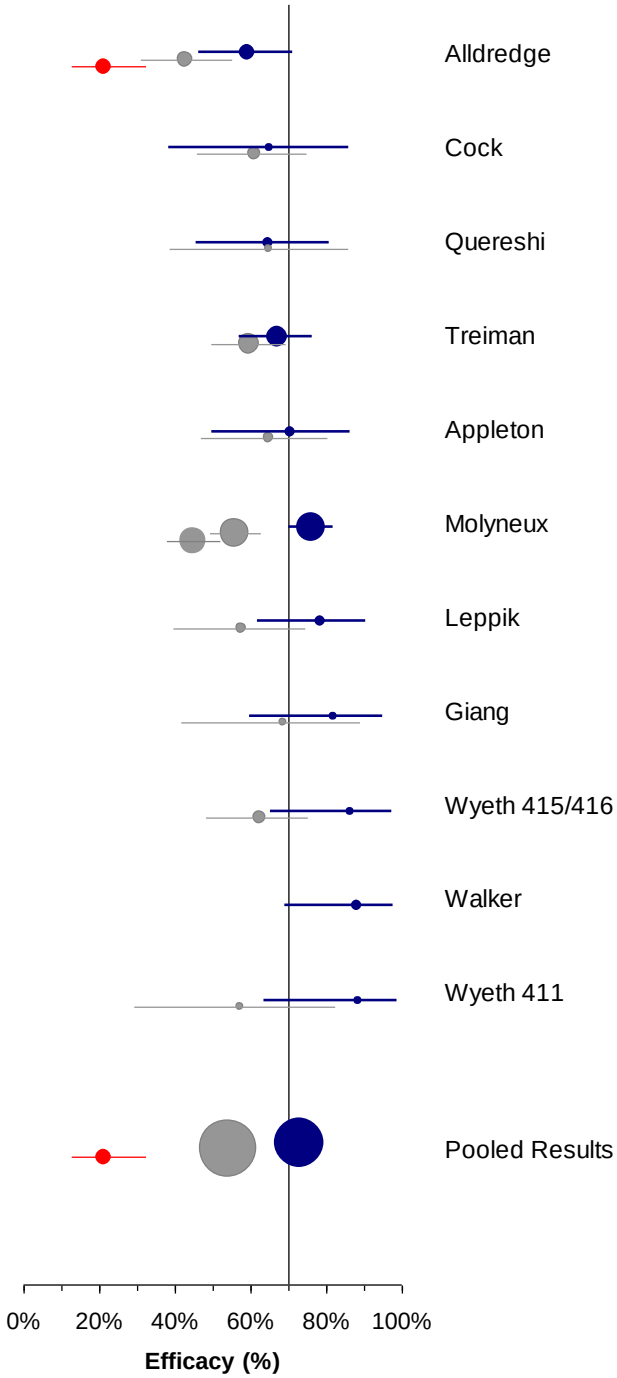
NETT


EMS

Study materials





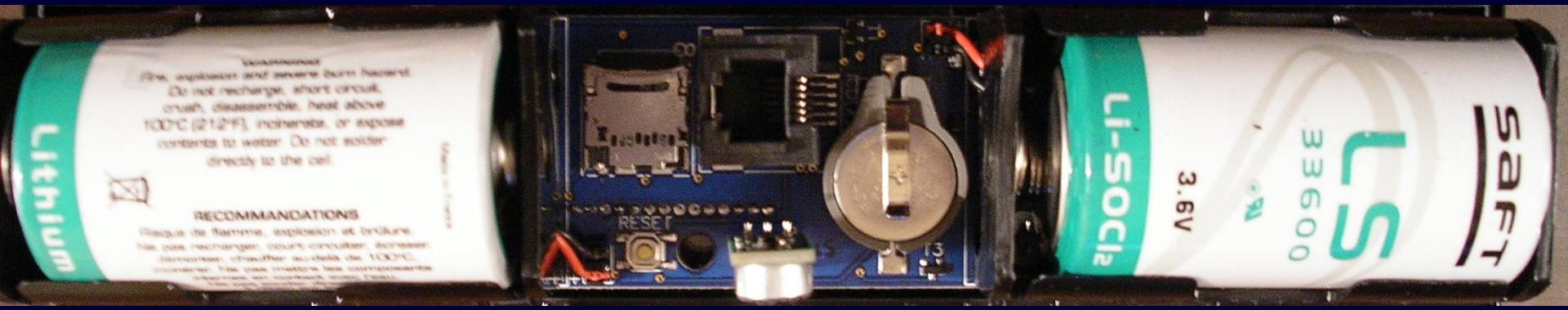

Alldredge
Cock
Quereshi
Treiman
Appleton
Molyneux
Leppik
Giang
Wyeth 415/416
Walker
Wyeth 411
Pooled Results
0%
20%
40%
60%
80%
100%
Efficacy (%)

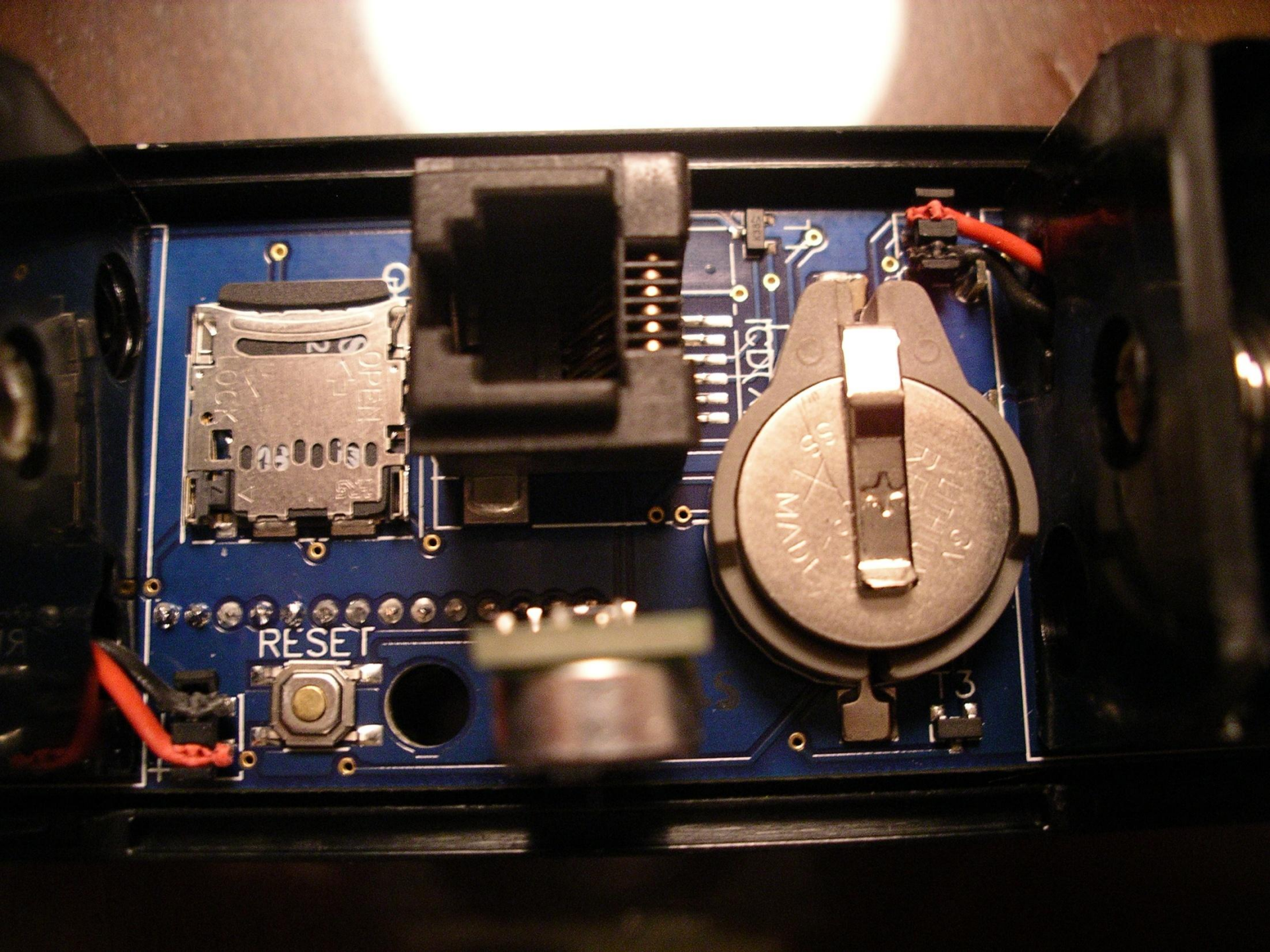
RAMPART

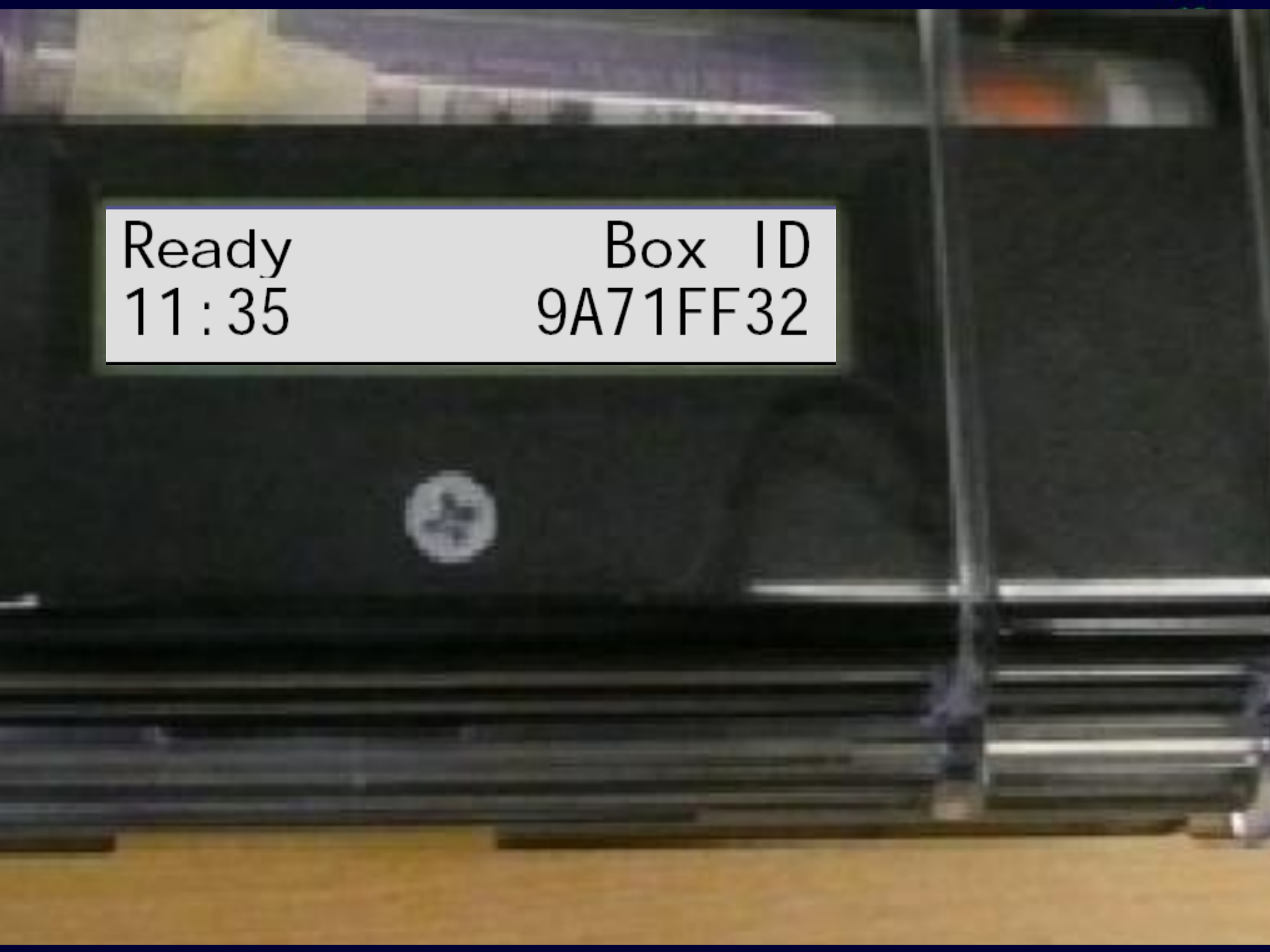
The Rapid Anticonvulsant Medications Prior toArrival Trial

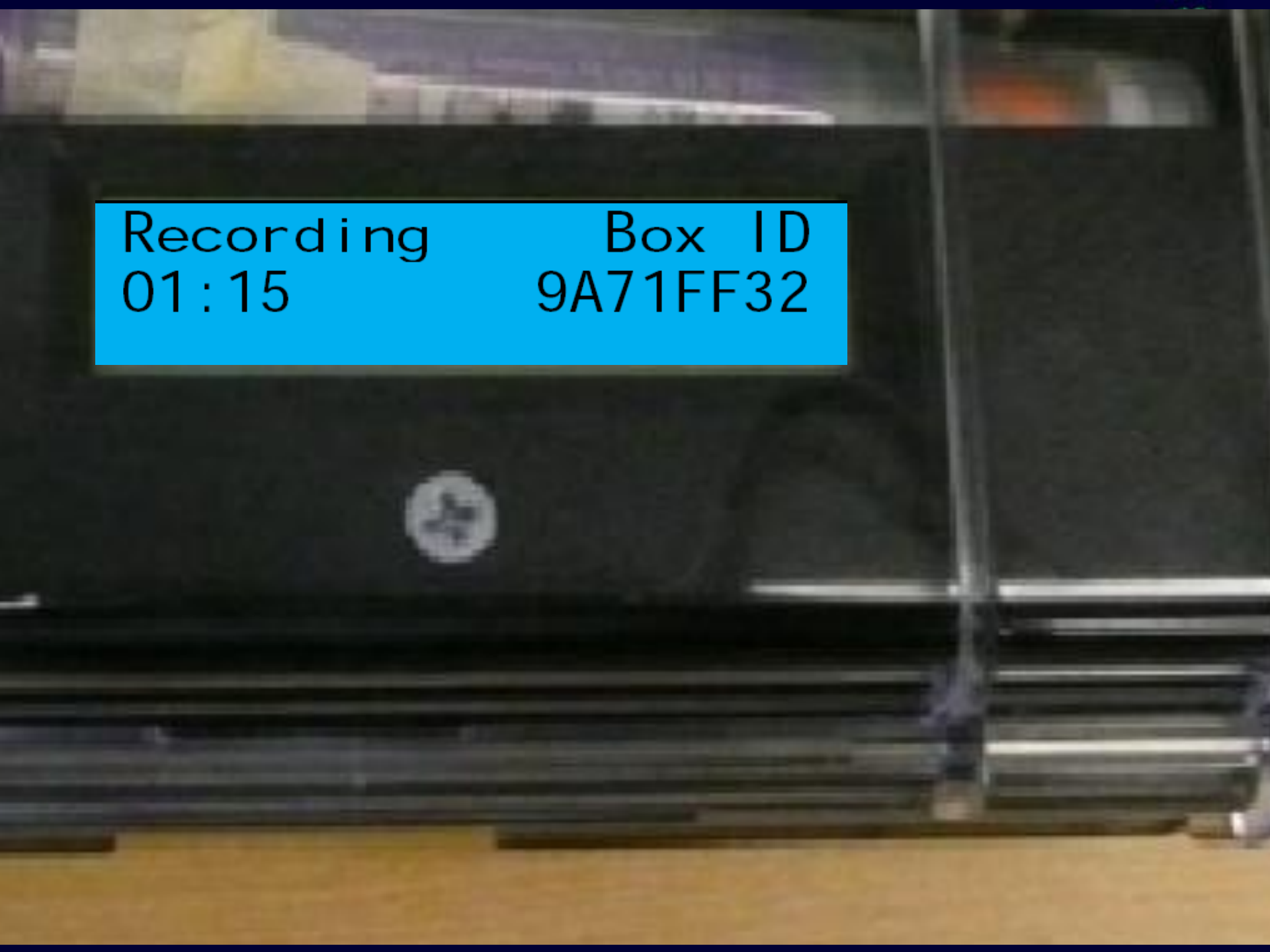
Finished at 19:54

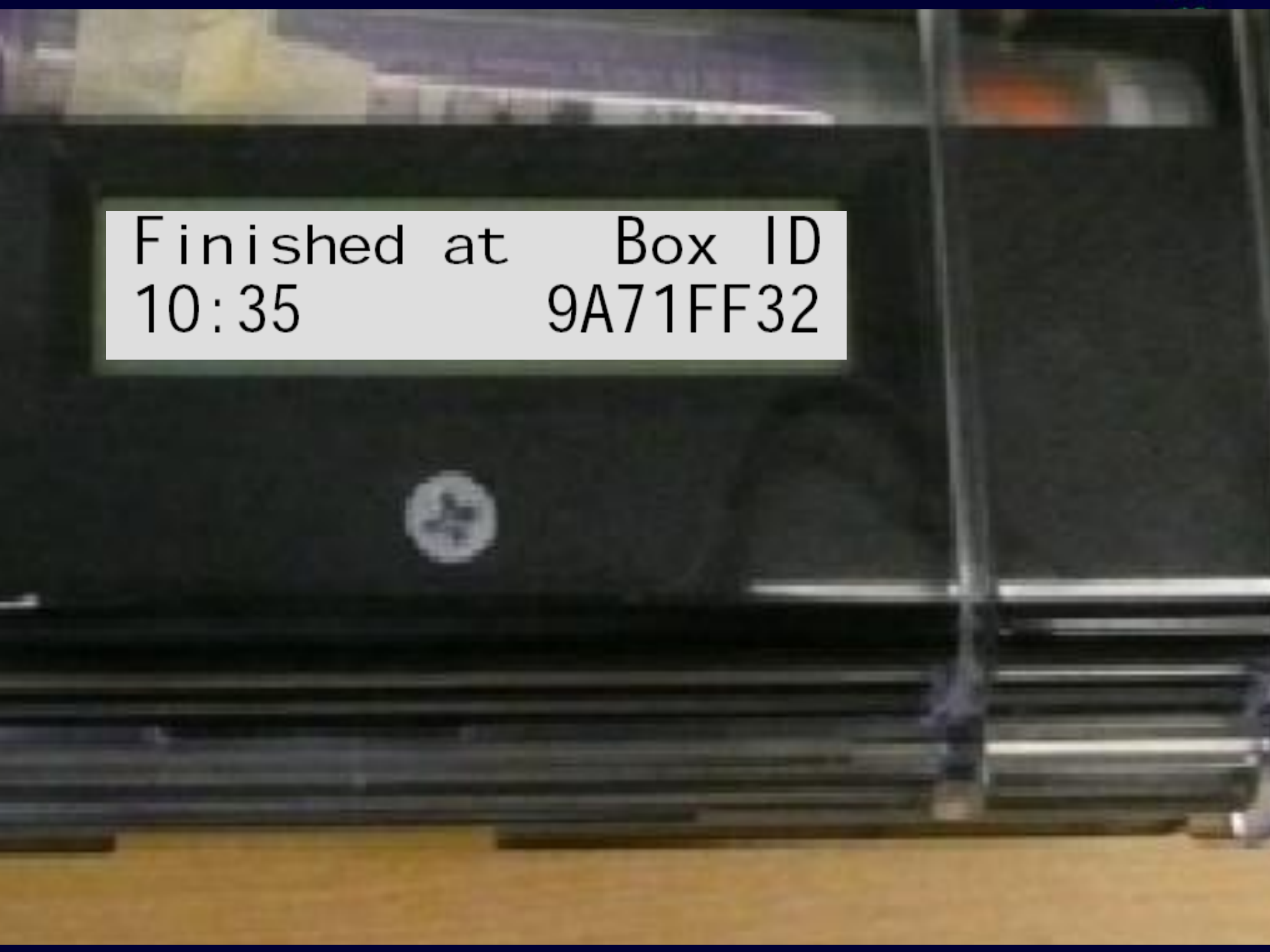
Box I B788CA6


Lithium
RECOMMANDATIONS
RESET
Li-SOCl2
3.6V
LS
3600
saft


RESET
OPEN
T3


Ready
11:35
Box ID
9A71FF32

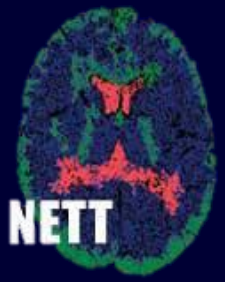

Recording
01:15
Box ID
9A71FF32


Finished at
10:35
Box ID
9A71FF32

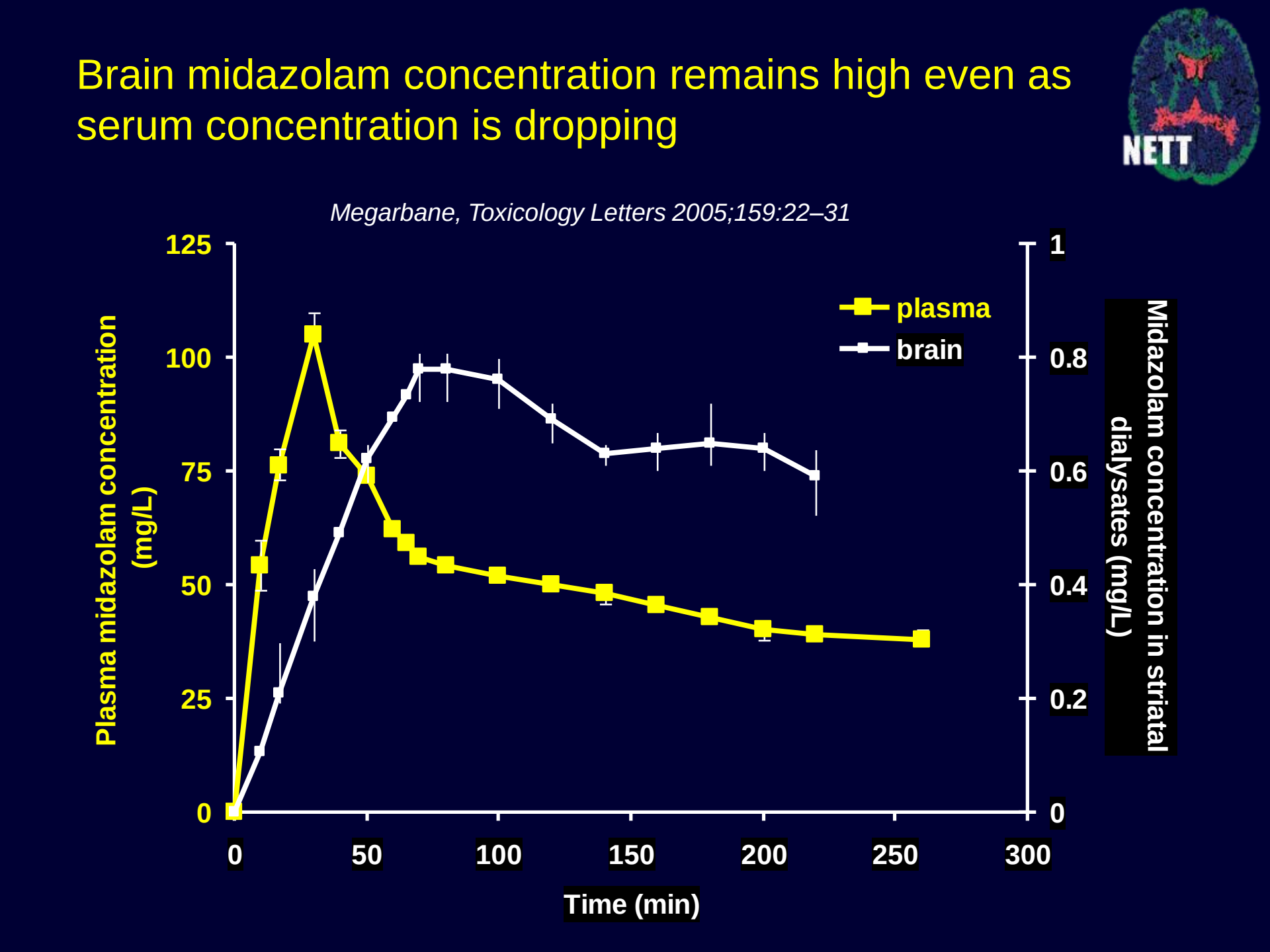

60day/temp
Box ID
04:25
9A71FF32

MADE IN CHINA


EMERGENCY!

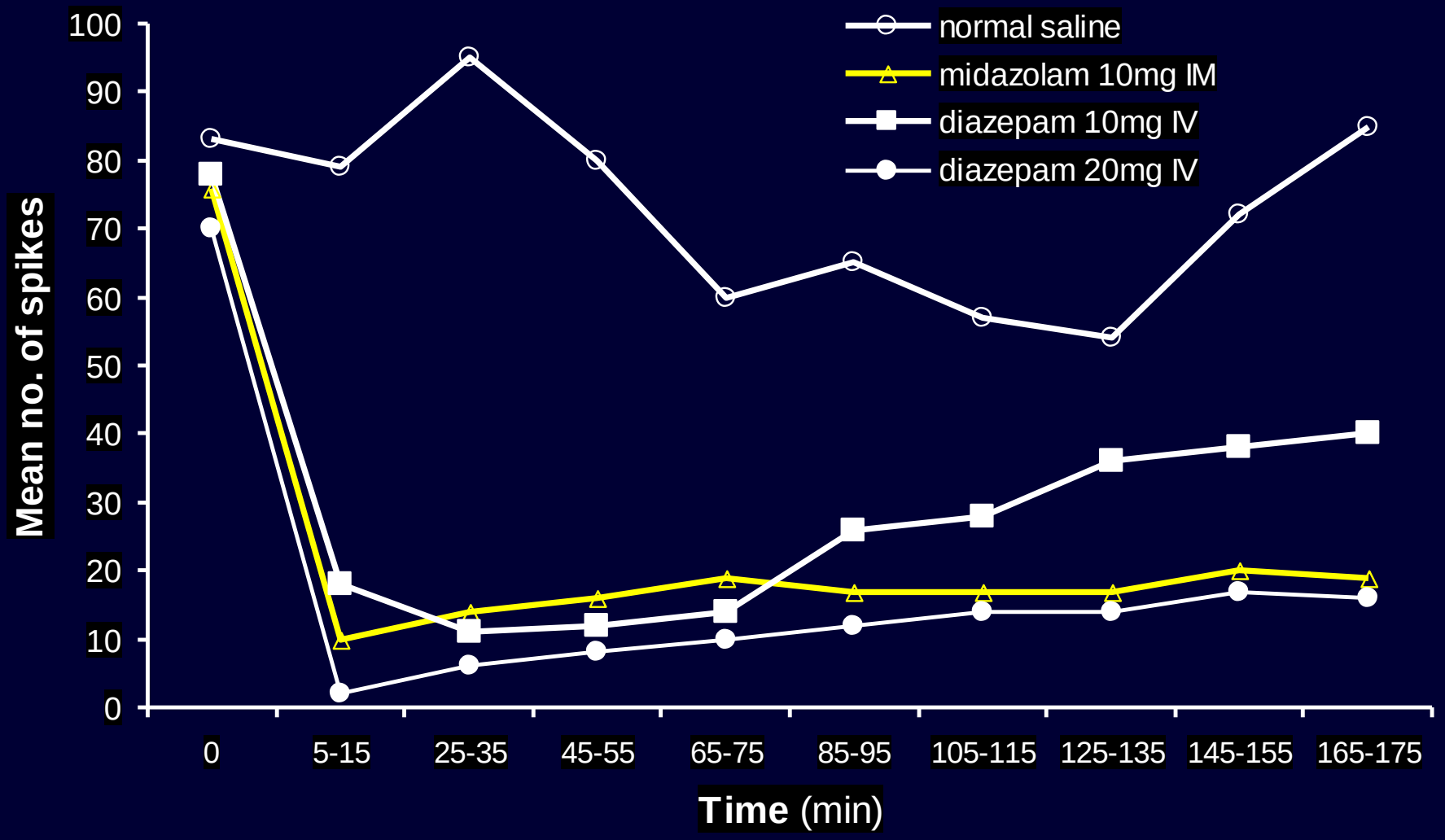

NETT

Brain midazolam concentration remains high even as serum concentration is dropping



Duration of seizure suppression with midazolam is hours, and similar to that of diazepam

Towne, J Emerg Med 1999;17:323–328



Time interval data

Still in rough analysis

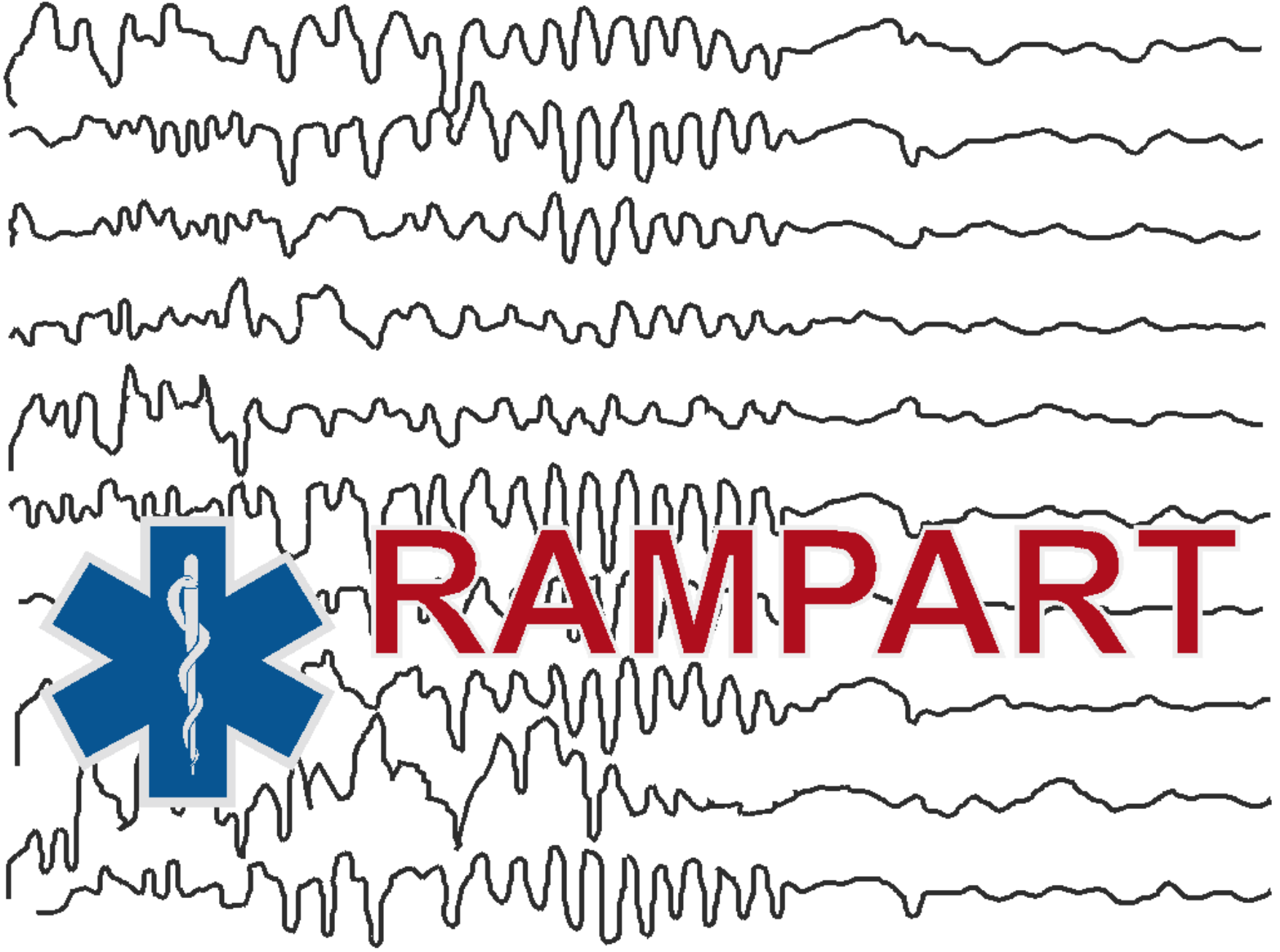
Time	Median (minutes)
Est. vehicular arrival on scene to box open	8.0
Box open to active drug	1.7
Active drug to seizure cessation	2.6

Intervention

- Two packages in each box, Child dose and Adult dose
- Each package has one IM injector, one IV dose, one of which is active, the other is dummy

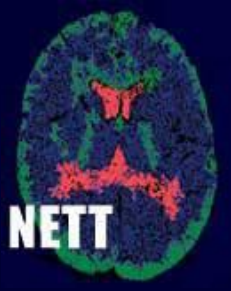
- Child (13- 39 kg) – Lorazepam 2 mg or Midazolam 5 mg
- Adult (40 kg and up)– Lorazepam 4 mg or Midazolam 10 mg

- Midazolam is in an autoinjector
- Lorazepam is given IV



The Rapid Anticonvulsant Medications Prior to Arrival Trial

Synergism



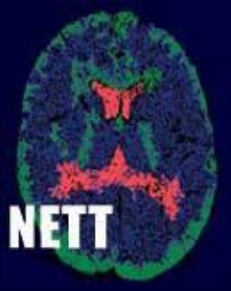
- Midazolam (MDZ) has rapid absorption and onset of action after intramuscular (IM) delivery than diazepam and other anticonvulsants.

- Important to CounterACT

- Important in clinical EMS practice

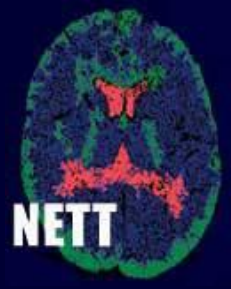
COUNTER ACT | Countermeasures Against Chemical Threats

CounterACT Executive Summary
Importance



- Importance to CounterACT
  - The advanced anticonvulsant system (AAS), an autoinjector containing midazolam, is meant to improve outcomes from nerve agent exposures when included with pralidoxime and atropine autoinjectors, but it requires clinical testing for FDA approval.
  - Testing in the EMS environment is relevant to use in homeland security and military applications.

CounterACT Executive Summary
Importance



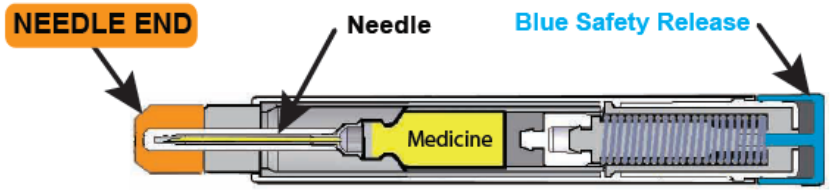
- Importance to clinical practice
  - 200,000 cases of status epilepticus in the US every year resulting in as many as 55,000 deaths
  - Existing prehospital treatments are suboptimal
  - A midazolam IM autoinjector promises to benefit patients treated by paramedics for status epilepticus (SE) in routine prehospital clinical practice where the administration of intravenous (IV) agents is complicated by the risk and difficulty of starting venous access in convulsing patients in environments that are usually poorly controlled

Investigational Auto-Injector

CAUTION: Never touch the orange **NEEDLE END!**

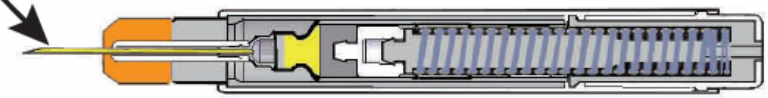
IMPORTANT: Do Not Remove **BLUE SAFETY RELEASE** until ready to use.

Investigational Auto-Injector



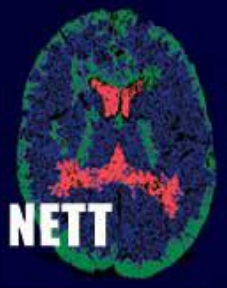
Inside view of auto-injector

Exposed needle of a used auto-injector



Inside view of used auto-injector

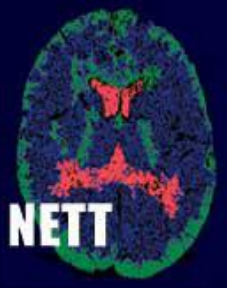
Foundational principles of the plan:



these are the underlying ethical purposes that we infer from the rules at 21 CFR 50.24. We use these as the goals to meet to define successful implementation. These principles are:

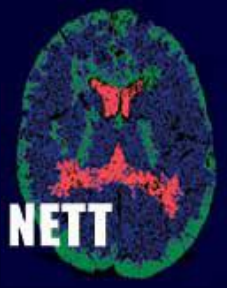
- Understanding
- Respect
- Transparency

Understanding



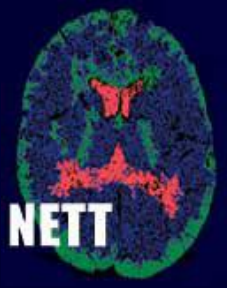
- the information we wish to obtain from community consultation is the variety of values and narratives of the people to whom we talk. The research to be conducted is the stimulus for the discussion, but the goal is for us to better understand them.

Respect



- local investigators will demonstrate respect by going to community gatherings to make presentations, rather than by asking the community to come to us. The process is one of humility that emphasizes personal interaction.

Transparency



- public notification is about having nothing to hide. Adequacy is determined by the fullness of disclosure and the ease of accessibility rather than a head count of recipients or viewers.

Status Epilepticus at the Time of Emergency Department Arrival

Alldredge et al. N Engl J Med 2001;345:631-7.

Variable	LORAZEPAM (N=66)	DIAZEPAM (n=68)	PLACEBO (n=71)
	% of patients		
SE terminated	59.1	42.6	21.1
Ongoing SE	40.9	57.4	78.9

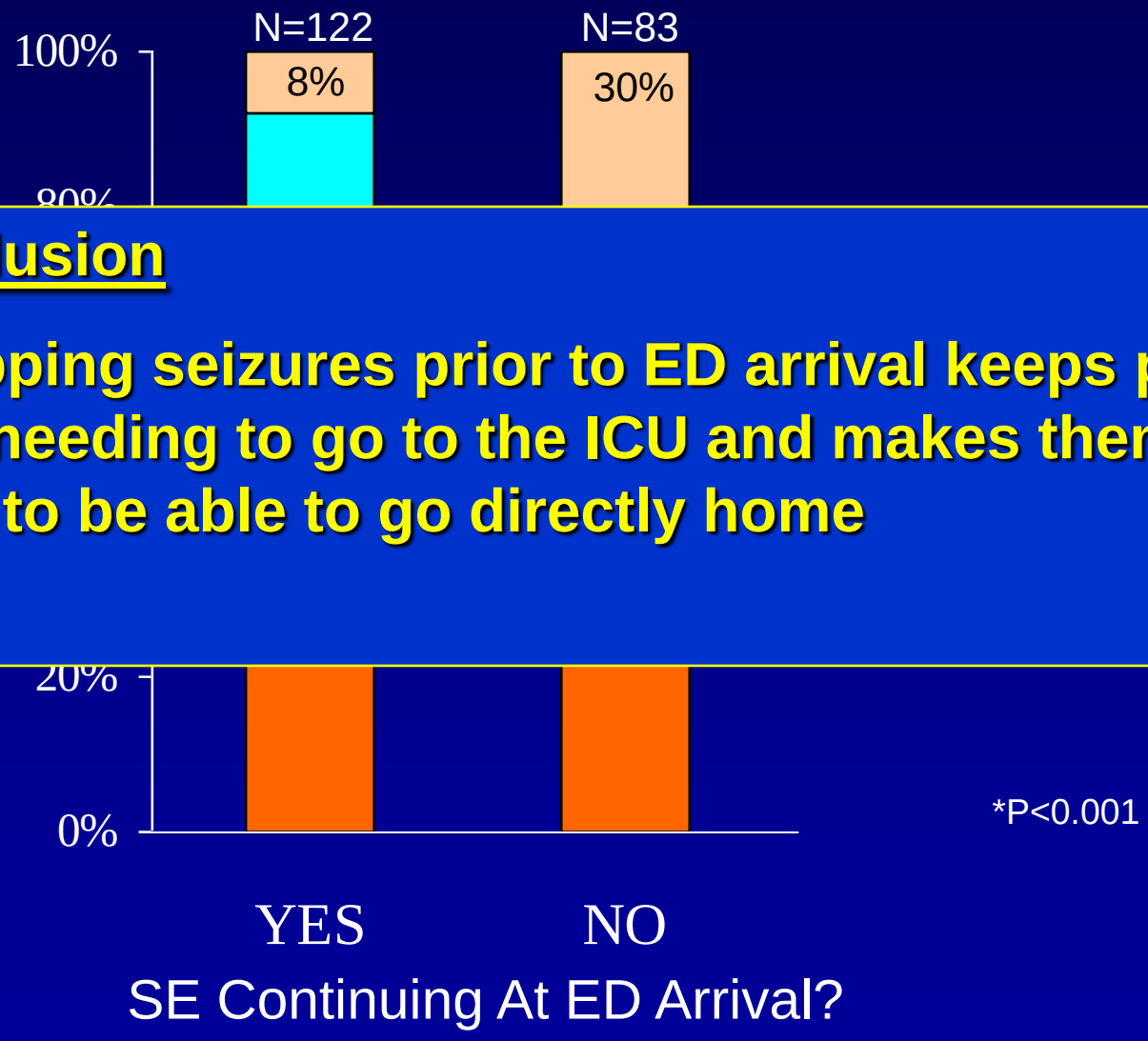
Conclusion

- **Lorazepam and diazepam better than placebo**
- **Lorazepam probably better than diazepam**

Odds ratios adjusted for ethnicity, interval from SE onset to study treatment and from study treatment to ED arrival, and cause of SE within prognostic group

Disposition of Patients from the Emergency Department

Alldredge et al. N Engl J Med 2001;345:631-7.

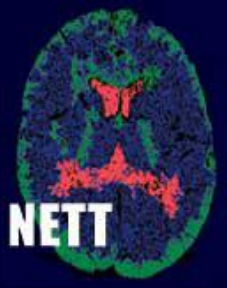


Conclusion

- **Stopping seizures prior to ED arrival keeps patients from needing to go to the ICU and makes them more likely to be able to go directly home**

Synopsis - double-dummy design

All subjects get active treatment by either IM or IV route



Randomized to:	IM Active Treatment	or	IV Active Treatment
IM Route	**Autoinjector midazolam**		**Autoinjector placebo**
	+		+
IV Route	**IV syringe placebo**		**IV syringe lorazepam**

Purpose

- We need to be…

  Heedful
  Respectful
  Transparent
  Humble

Purpose

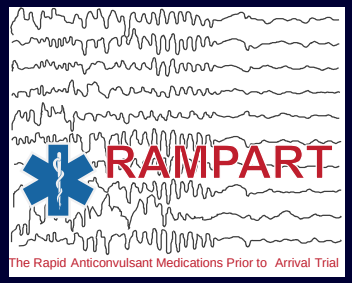
- We need to be…

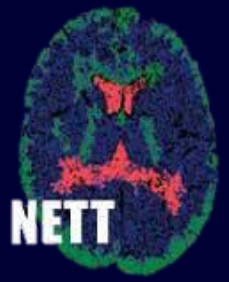
Heedful	⇨	Comm. Consult.
Respectful	⇨	Comm. Consult.
Transparent	⇨	Public Disclosure
Humble	⇨	Comm. Consult.

Purpose

- We need to be…

Heedful	⇨	Listen and consider
Respectful	⇨	Go to the people
Transparent	⇨	Keep nothing concealed
Humble	⇨	Do it yourself





Neurological Emergencies Treatment Trials (NETT)

Intramuscular midazolam v. intravenous lorazepam in the pre-hospital treatment of status epilepticus: the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)

This work was primarily supported by award 5U01NS056975-04 from the National Institute of Neurological Disorders and Stroke (NINDS), the Office of the Director, National Institutes of Health (OD), BARDA, and the NIH CounterACT program

Enrollment

- First subject in 6/15/2009

Importance

- Importance to clinical practice
  - 200,000 cases of status epilepticus in the US every year resulting in as many as 55,000 deaths
  - Existing prehospital treatments are suboptimal
  - A midazolam IM autoinjector promises to benefit patients treated by paramedics for status epilepticus (SE) in routine prehospital clinical practice where the administration of intravenous (IV) agents is complicated by the risk and difficulty of starting venous access in convulsing patients in environments that are usually poorly controlled

Aims

Primary Hypothesis

- IM midazolam is as effective as IV lorazepam at stopping convulsions prior to ED arrival

Secondary Hypotheses

- Convulsions stop more rapidly with treatment with IM midazolam versus IV lorazepam
- There is no difference in safety between the two treatments

Primary Outcome

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Analysis† (N=893)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)
Primary outcome		
Seizures terminated, no rescue therapy given		
No. of subjects	329	282
% of subjects (95% CI)§	73.4 (69.3–77.5)	63.4 (58.9–67.9)
Treatment failed — no. of subjects (%)	119 (26.6)	163 (36.6)
Seizures not terminated, no rescue therapy given	50 (11.2)	64 (14.4)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)

Silbergleit R et al. N Engl J Med 2012;366:591-600

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Exception from Informed Consent Clinical Trials in the Neurological Emergencies Treatment Trials (NETT)

1U01NS056975-01

Robert Silbergleit
NETT Clinical Coordinating Center
University of Michigan, Ann Arbor

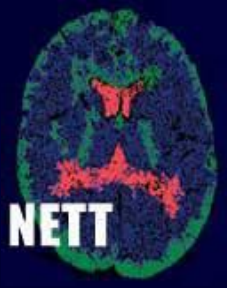
Objectives

NETT EFIC Clinical Trials

The NETT Approach to EFIC

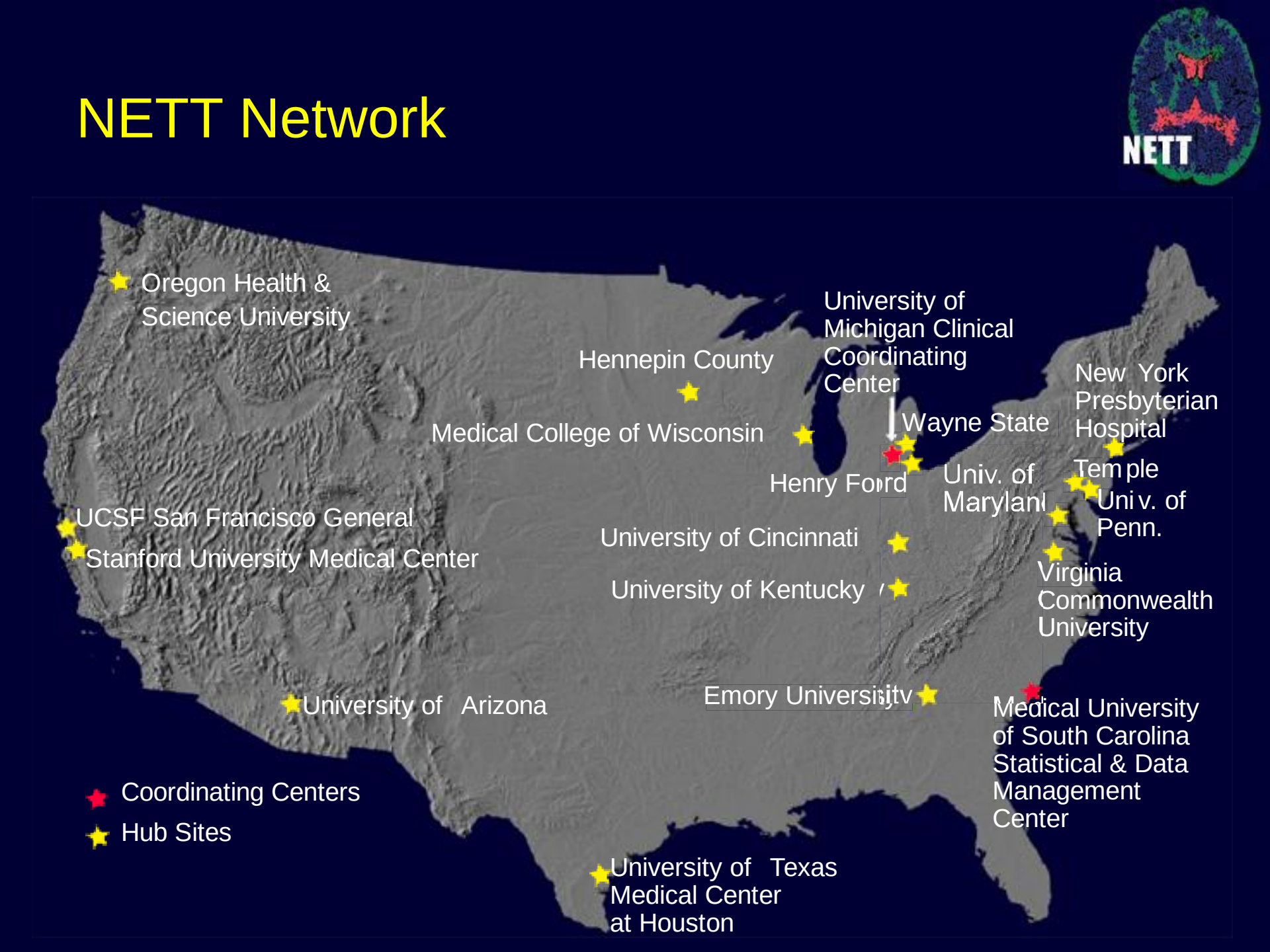
Our Experience

Orientation to the NETT

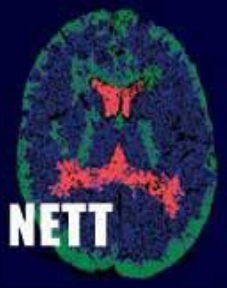


- Created in 2007
- ED oriented but multidisciplinary
- 17 Hubs, CCC, SDMC, NINDS

NETT Network



Orientation to the NETT



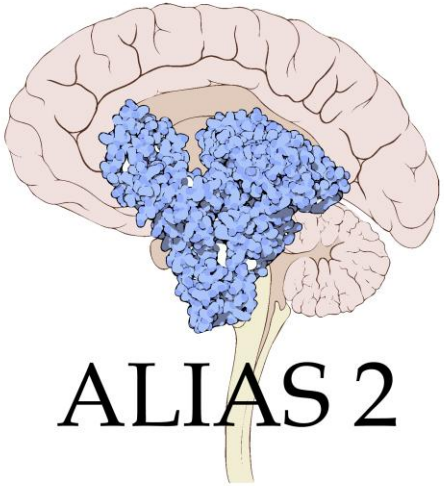
- Funded infrastructure
- Trials supported by independent grants
- Goal is a full pipeline

NETT

RAMPART

The Rapid Anticonvulsant Medications Prior to Arrival Trial

ProTECT™



ALIAS 2

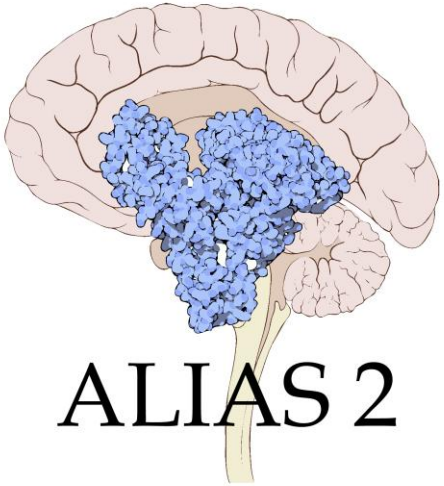
point

NETT

RAMPART

Rapid Anticonvulsant Medications Prior to Arrival Trial

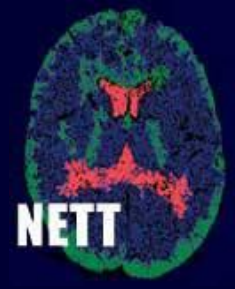
ProTECT™



ALIAS 2

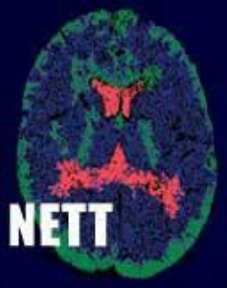
point

In the pipeline



- SHINE
- ARCTIC
- ESETT
- Duration of Hypothermia after Cardiac Arrest
- And many more in earlier stages…..

NETT Approach to EFIC



- Promoting collegiality and collaboration within and between clinical sites
- Providing centralized resources and coordination while respecting local control

NETT Approach to EFIC

- Promoting collegiality and collaboration within and between clinical sites
  - **Bringing people together**
  - Human subjects protection coordinator
  - Network HSP working group

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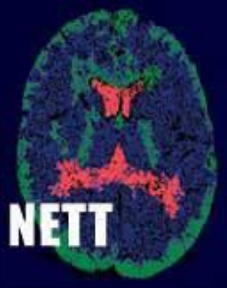

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NETT Approach to EFIC

- Providing centralized resources and coordination while respecting local control
  - **Shared resources**
  - Standardized reporting
  - Information technology

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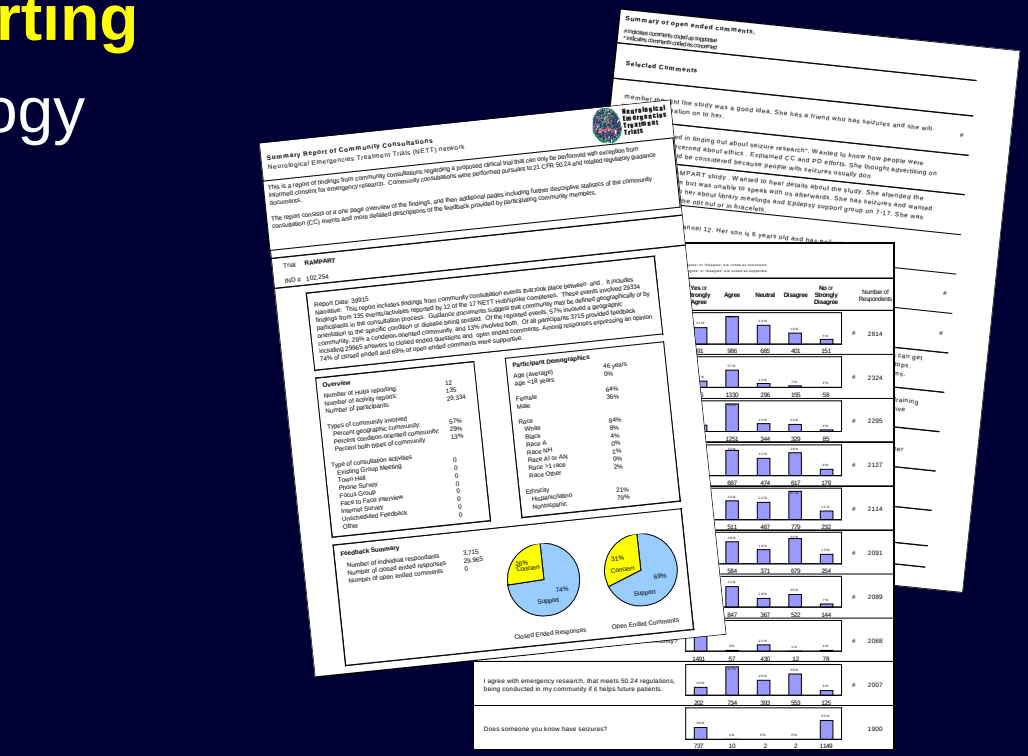

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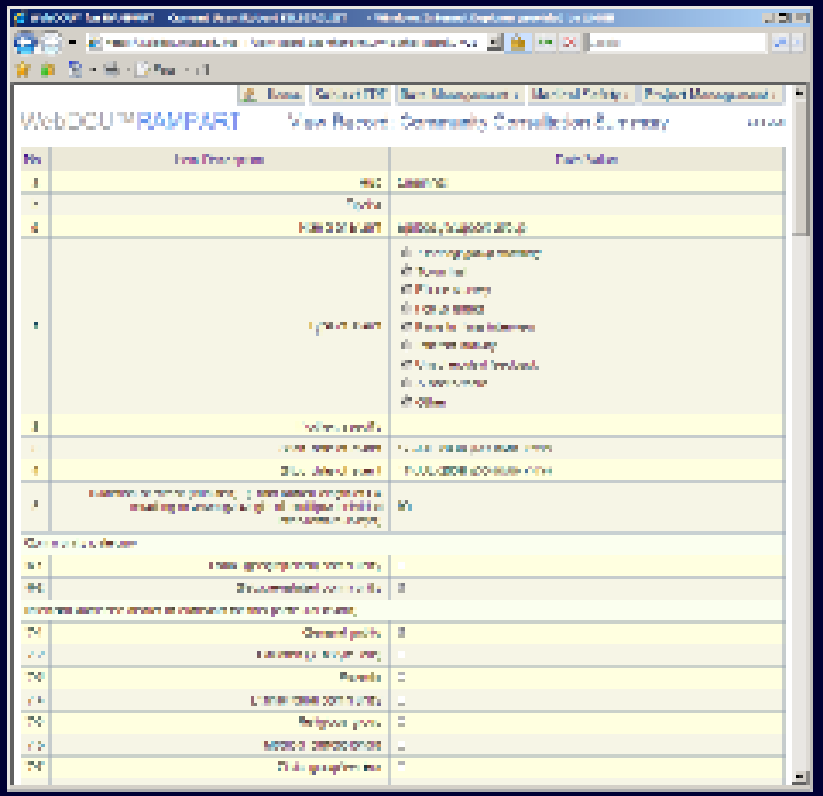
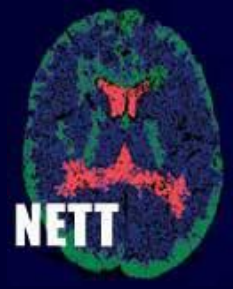
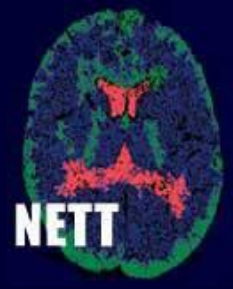


Our Experience - RAMPART



- 43 IRB’s for 321 entities
- Submission of local EFIC plan to beginning enrollment ranged from 2 to 22 months with mean and median of 11 months
- 1 municipal IRB reviewed and did not approve

Our Experience - RAMPART



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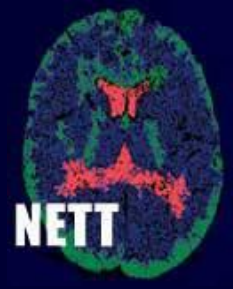

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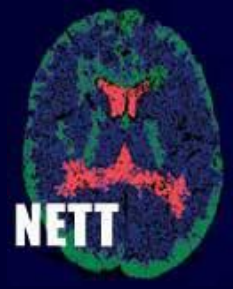
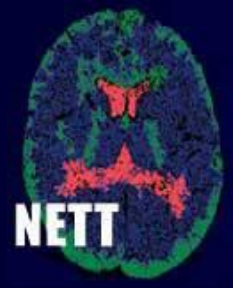


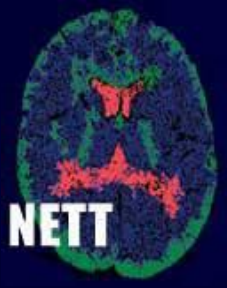
- 225 Community Consultation activities
- 23,898 participants
- Feedback from 6,846 individuals
  - 50,275 closed ended responses
  - 2,635 open ended responses and comments
  - 78% supportive on qualitative coding

Our Experience - RAMPART



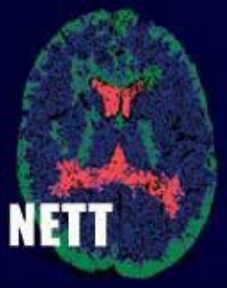
- visits to existing group meetings (43%)
- focus groups / interviews (19%)
- booth or table at events (8%)
- town hall meetings (9%)
- random digit dialing or internet surveys (4%)
- call-in radio talk shows (1%)
- unscheduled feedback (phone calls, e-mail, etc.)

Our Experience - RAMPART



- geographical communities (68%)
- seizure risk-related communities (32%)

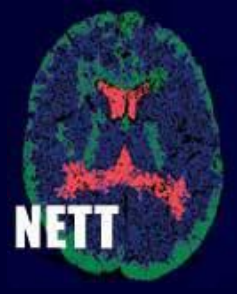
Our Experience - RAMPART



- general public (56%)
- parents (13%)
- children (8%)
- medical professionals (19%)
- ethnic or racial (6%)
- religious (2%)
- civic leaders (8%)
- and others

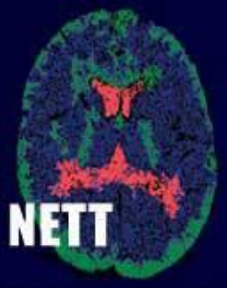
adds up to more than 100% because some events involved multiple categories of participants

Our Experience - RAMPART

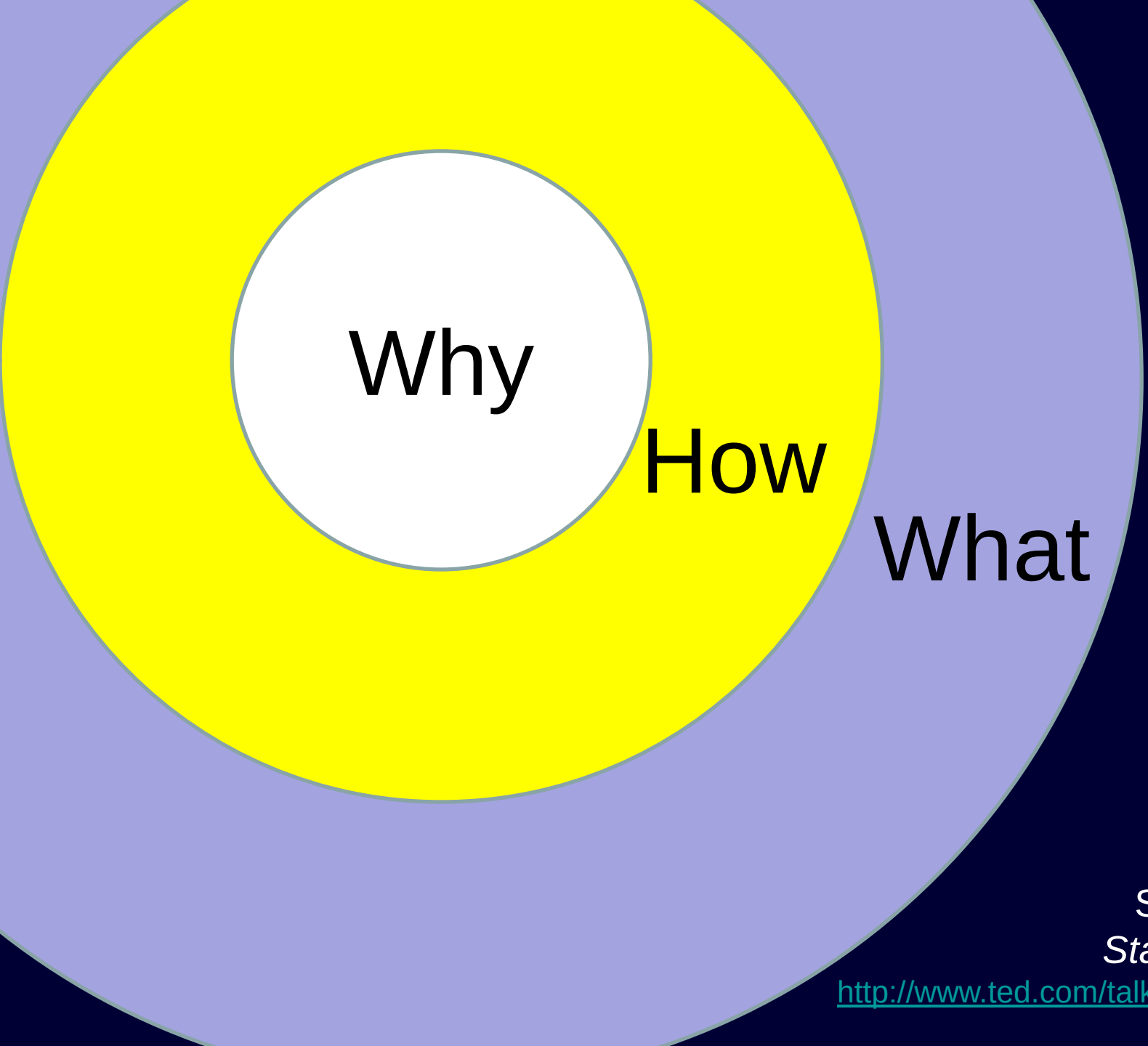


- 289 public disclosure activities pre/early trial
- newspaper stories or announcements in 18%
- radio and television broadcasts in 10%
  - 75% of the estimated audience from these
- Electronic media (e-mail / website) 19%
  - 11% of the estimated audience
- brochures, posters, fliers, direct mailings, billboards, information booths, presentations, and other communications.

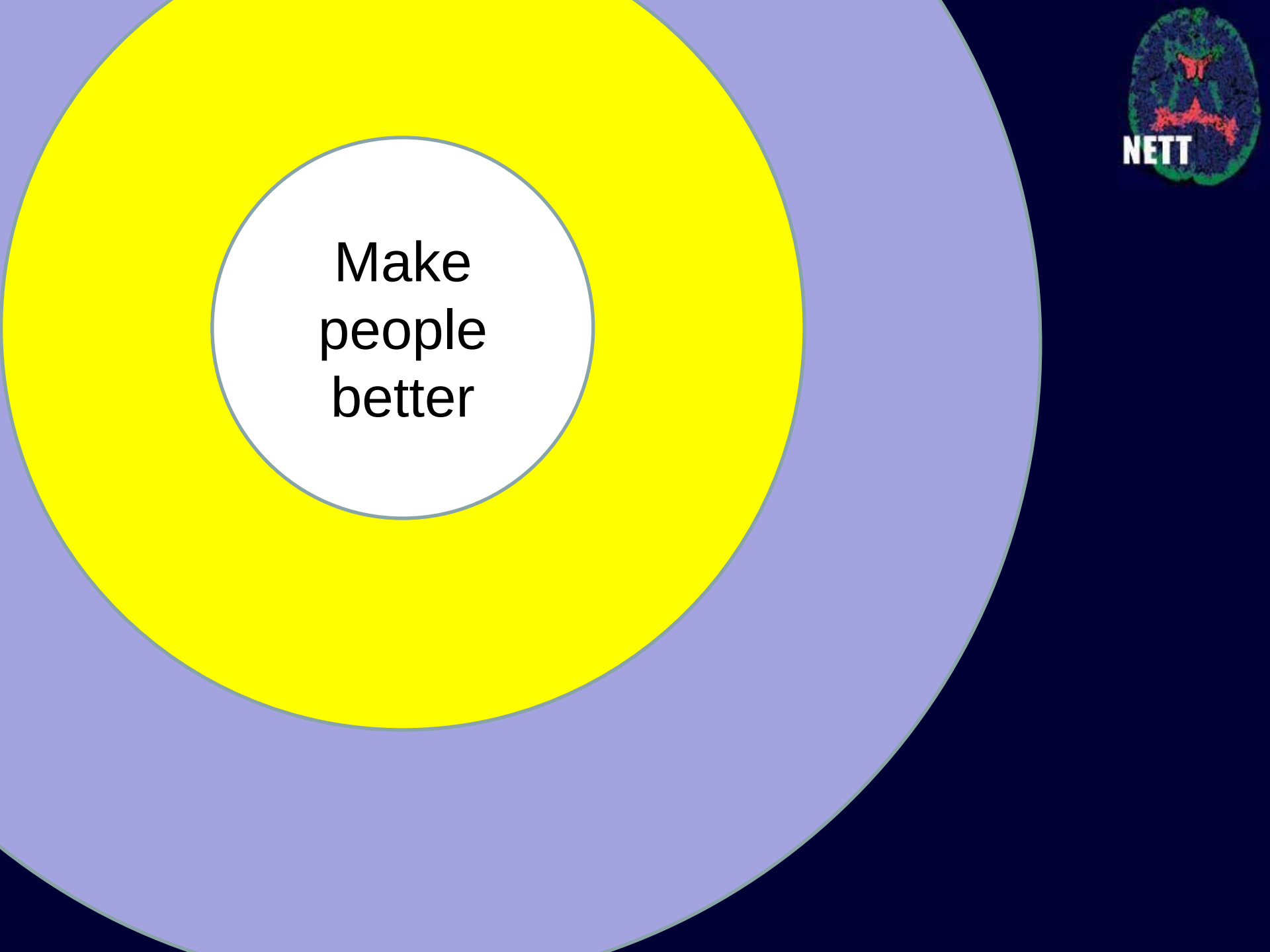
Our Experience - ProTECT

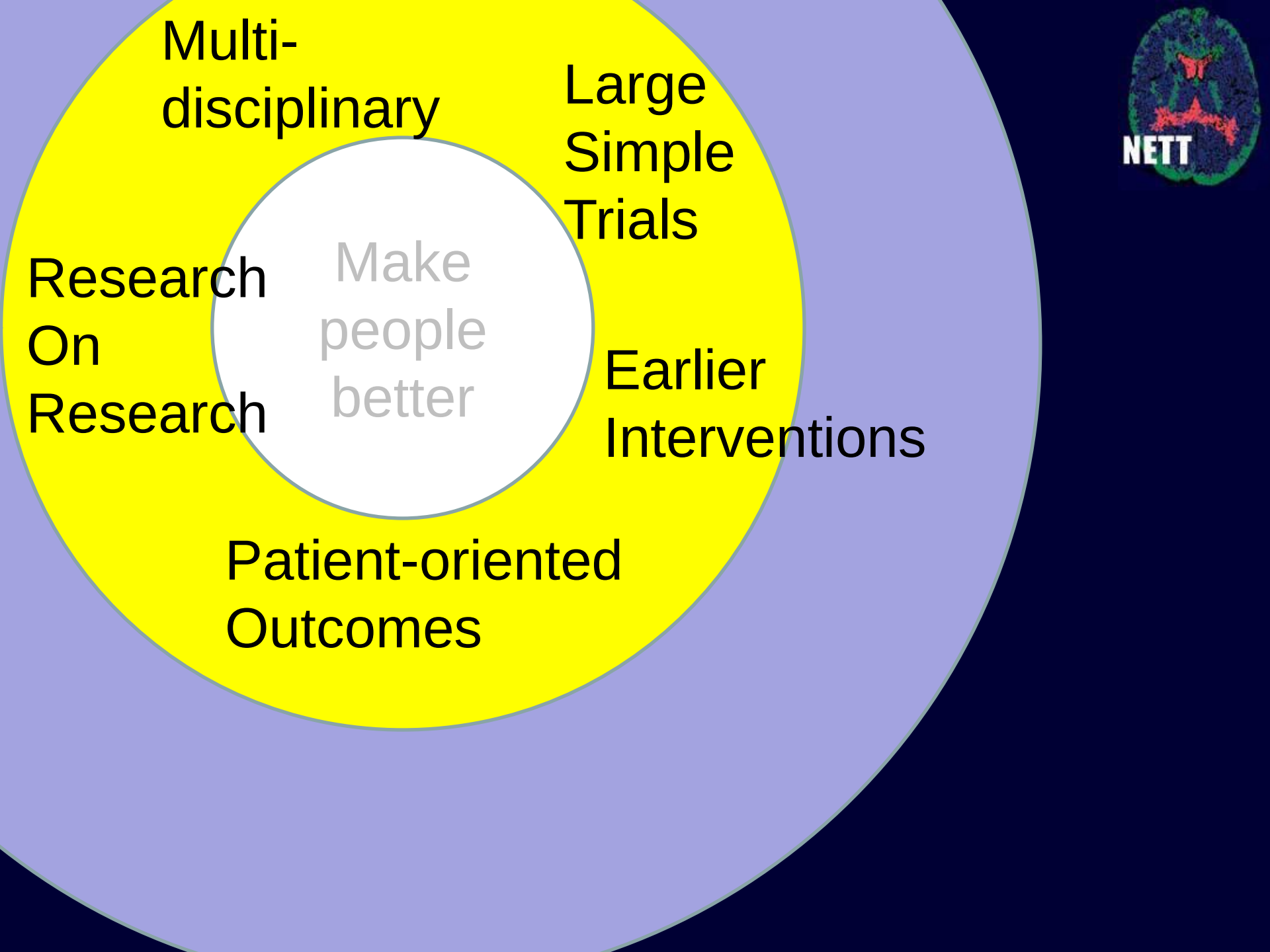


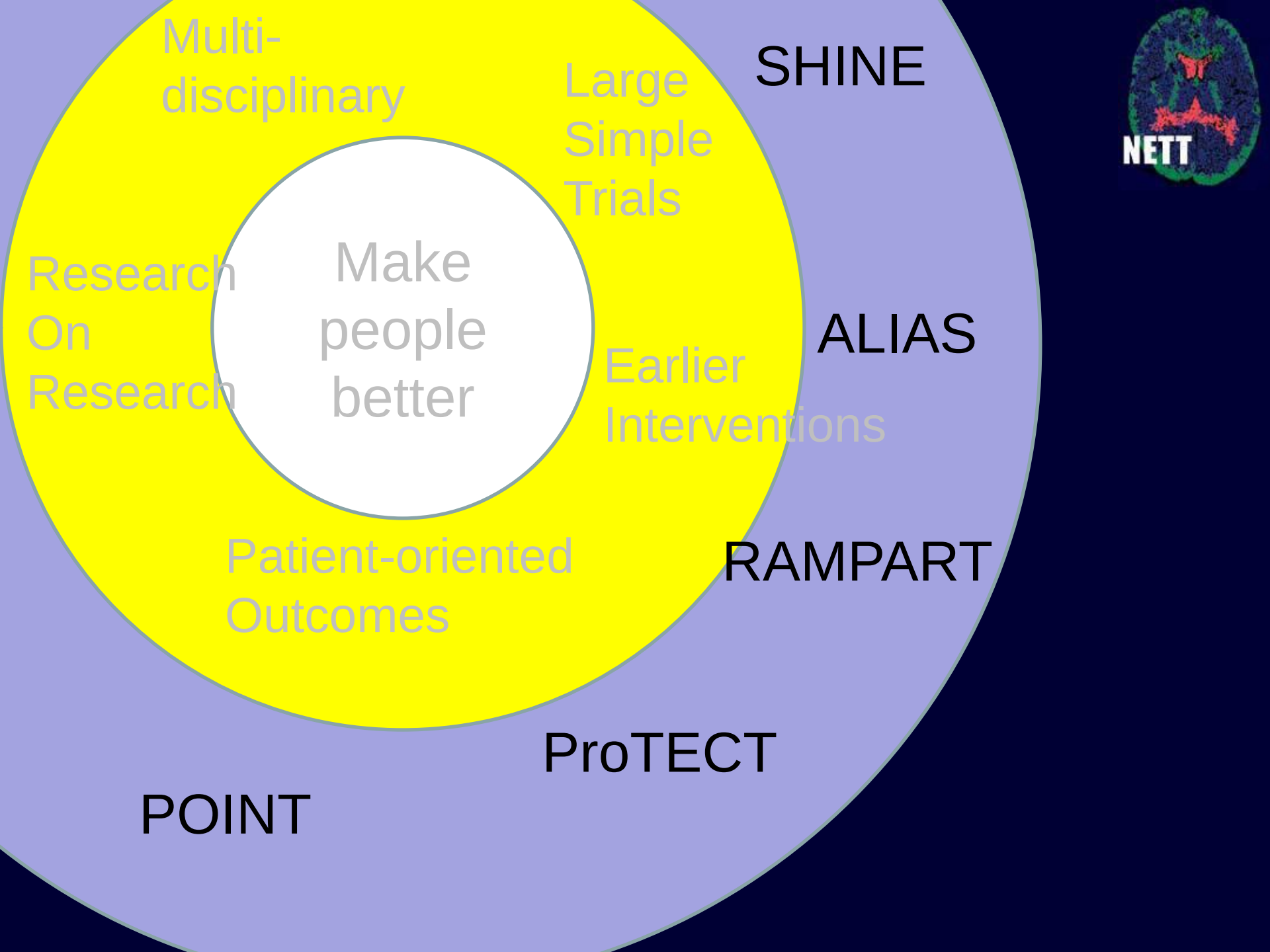
- EFIC processes and approvals came quicker
- Evaluations made more consistent across sites
- PEER-ProTECT built on PEER-RAMPART



Simon Sinek
Start with Why
http://www.ted.com/talks/simon_sinek


Make
people
better


Multi-
disciplinary
Large
Simple
Trials
Research
On
Research
Make
people
better
Earlier
Interventions
Patient-oriented
Outcomes
NETT


Multi-
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SHINE
NETT
Research
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Make
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ALIAS
Earlier
Interventions
Patient-oriented
Outcomes
RAMPART
ProTECT
POINT

A large simple trial….

“What is written without effort is in general read without pleasure.”

Samuel Johnson

Or…..

Simple ≠ Easy

Baseline Characteristics

Table 1. Characteristics of the Subjects at Baseline.*

Characteristic	IM Midazolam (N=448)	IV Lorazepam (N=445)
Age		
Mean (range) — yr	43±22 (0–102)	44±22 (1–94)
Age group — no. (%)		
0–5 yr	32 (7)	29 (7)
6–10 yr	15 (3)	20 (4)
11–20 yr	28 (6)	21 (5)
21–40 yr	114 (25)	112 (25)
41–60 yr	169 (38)	169 (38)
≥61 yr	90 (20)	94 (21)
Male sex — no. (%)	250 (56)	238 (53)
Race — no. (%)†		
Black	229 (51)	224 (50)
White	165 (37)	183 (41)
Other, mixed, or unknown	54 (12)	38 (9)
Ethnic group — no. (%)†		
Non-Hispanic	310 (69)	290 (65)
Hispanic	49 (11)	57 (13)
Unknown	89 (20)	98 (22)

Table 1. Characteristics of the Subjects at Baseline.*

Characteristic	IM Midazolam (N=448)	IV Lorazepam (N=445)
Dose tier — no. (%)‡		
Low	62 (14)	59 (13)
High	386 (86)	386 (87)
History of epilepsy — no. (%)		
Yes	293 (65)	295 (66)
No	111 (25)	103 (23)
Not documented	44 (10)	47 (11)
Final diagnosis — no. (%)		
Status epilepticus	404 (90)	399 (90)
Nonepileptic spell	31 (7)	32 (7)
Undetermined	13 (3)	14 (3)
Precipitating cause of status epilepticus — no. (%)		
Noncompliance with or discontinuation of anticonvulsant therapy	137 (31)	141 (32)
Idiopathic or breakthrough status epilepticus	121 (27)	121 (27)
Coexisting condition that lowered seizure threshold	33 (7)	29 (7)

Primary Outcome

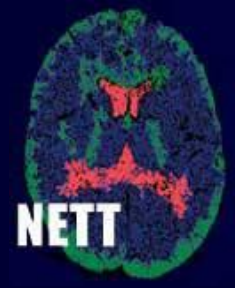

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Primary outcome				
Seizures terminated, no rescue therapy given				
No. of subjects	329	282	271	238
% of subjects (95% CI)§	73.4 (69.3–77.5)	63.4 (58.9–67.9)	74.9 (70.4–79.3)	64.3 (59.4–69.2)
Treatment failed — no. of subjects (%)	119 (26.6)	163 (36.6)	91 (25.1)	132 (35.7)
Seizures not terminated, no rescue therapy given	50 (11.2)	64 (14.4)	42 (11.6)	51 (13.8)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)	14 (3.9)	38 (10.3)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)	35 (9.7)	43 (11.6)

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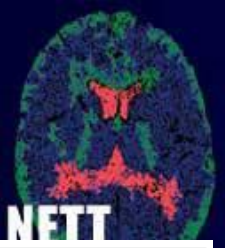
Secondary Outcomes



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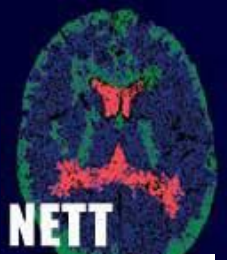
Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Secondary outcomes				
Endotracheal intubation within 30 min after ED arrival				
No. of subjects — %	63 (14.1)	64 (14.4)	53 (14.6)	53 (14.3)
Relative risk (95% CI)	0.98 (0.70–1.34)		1.02 (0.71–1.45)	
Hospitalization				
No. of subjects — %	258 (57.6)	292 (65.6)	210 (58.0)	250 (67.6)
Relative risk (95% CI)	0.88 (0.79–0.98)		0.86 (0.77–0.96)	
ICU admission				
No. of subjects — %	128 (28.6)	161 (36.2)	102 (28.2)	138 (37.3)
Relative risk (95% CI)	0.79 (0.65–0.95)		0.76 (0.61–0.93)	
Recurrent seizure within 12 hr after ED arrival				
No. of subjects — %	51 (11.4)	47 (10.6)	37 (10.2)	39 (10.5)
Relative risk (95% CI)	1.08 (0.74–1.56)		0.97 (0.63–1.48)	
Hypotension				
No. of subjects — %	12 (2.7)	13 (2.9)	5 (1.4)	9 (2.4)
Relative risk (95% CI)	0.92 (0.42–1.98)		0.57 (0.19–1.67)	

Secondary Outcomes (continued)



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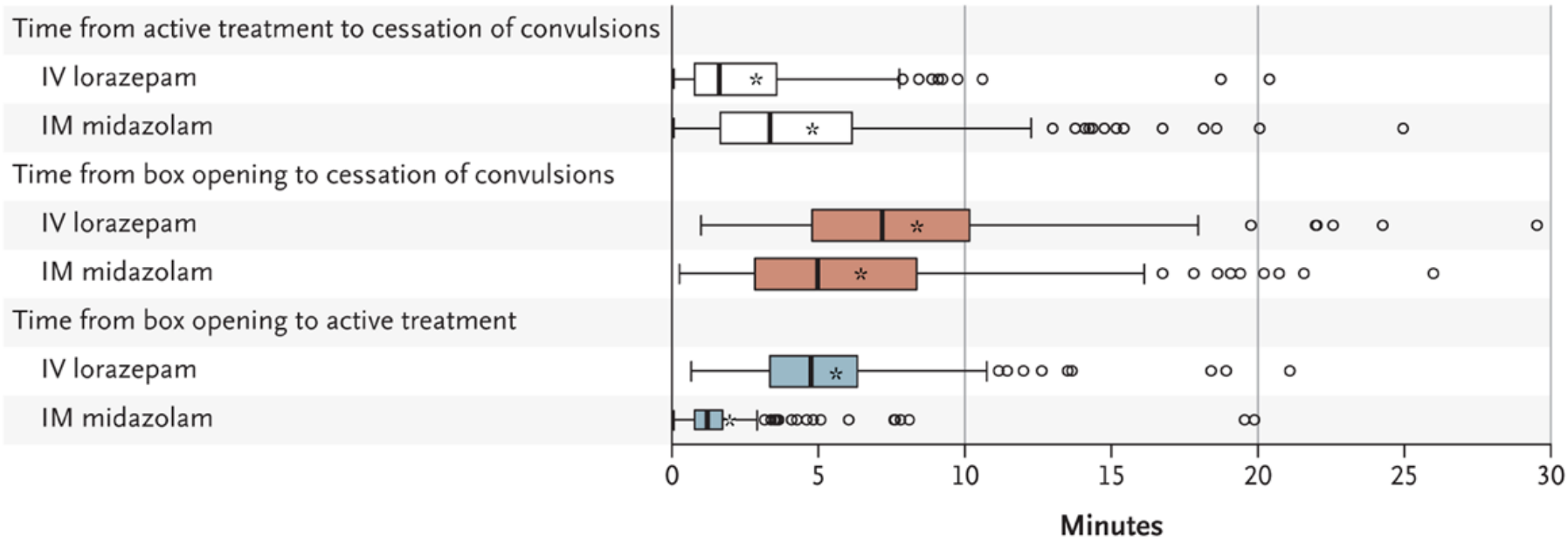
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Secondary outcomes				
IM injection-site complications				
No. of subjects (%)	4 (0.9)	2 (0.5)	4 (1.1)	1 (0.3)
Relative risk (95% CI)	1.99 (0.30–10.70)		4.09 (0.45–36.40)	
IV injection-site complications — no. of subjects (%)	0	3 (0.7)	0	3 (0.8)
Length of ICU stay — days				
No. of subjects with length-of-stay data	123	155	98	132
Mean	5.7±9.5	4.1±4.7	4.8±7.2	4.0±4.7
Median (minimum, maximum)	3 (1, 75)	3 (1, 31)	3 (1, 65)	2 (1, 31)
P value¶	0.09		0.33	
Length of hospital stay — days				
No. of subjects with length-of-stay data	251	285	204	243
Mean	6.7±10.0	5.5±6.4	5.8±7.0	5.5±6.4
Median (minimum, maximum)	4 (1, 90)	3 (1, 58)	3 (1, 65)	4 (1, 58)
P value¶	0.11		0.71	

Time Outcomes



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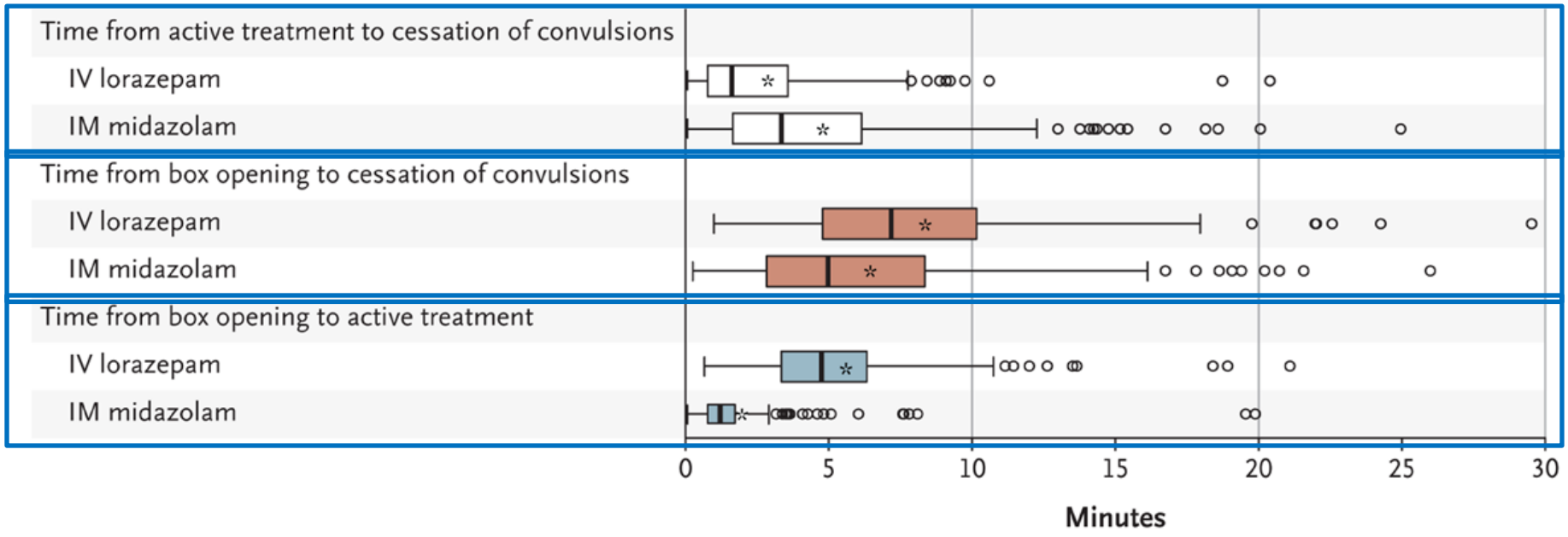
Time Outcomes



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