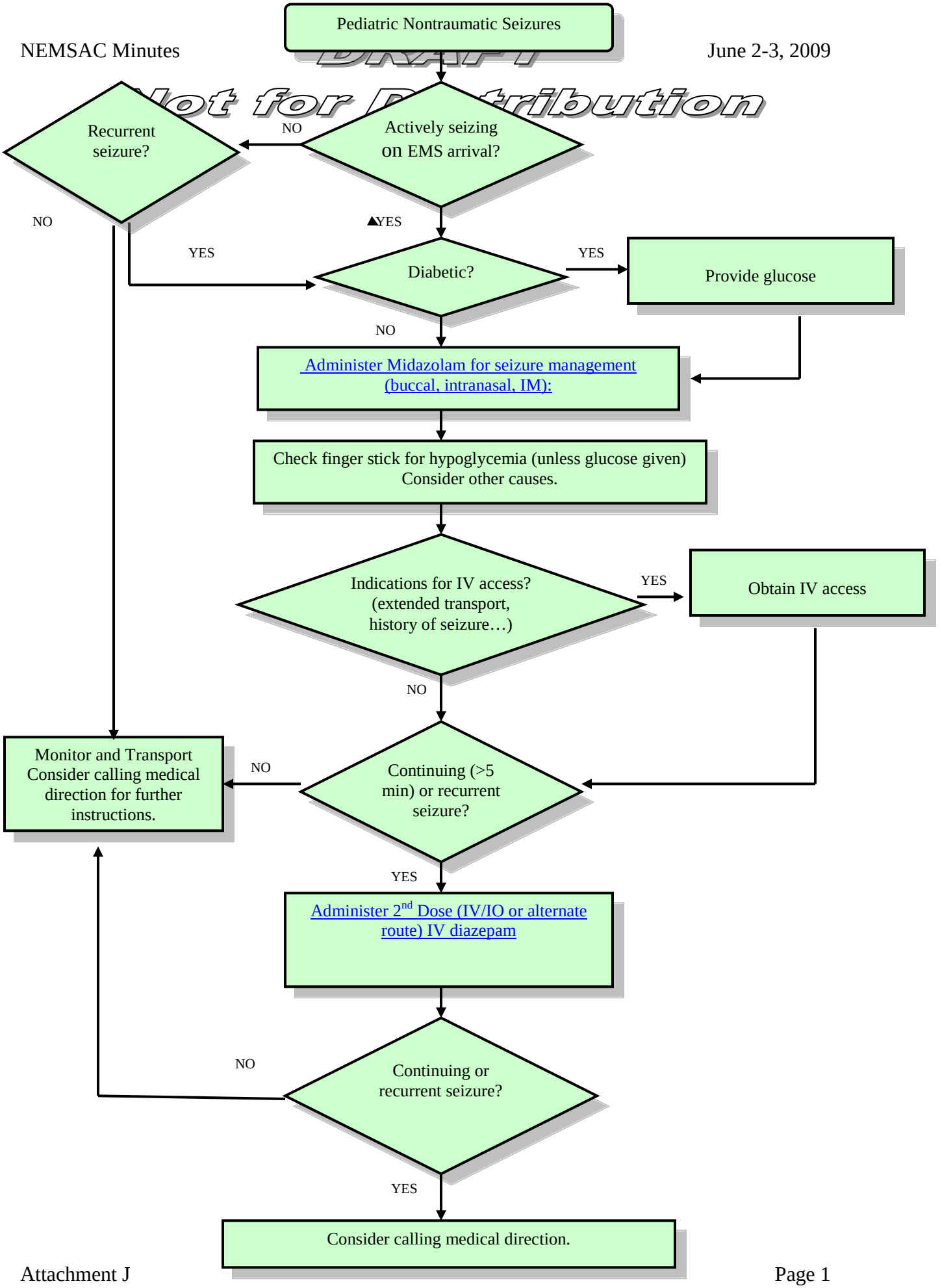

Administer Midazolam for seizure management (buccal, intranasal, IM):

List of Comparisons Contained Below:

1. **Buccal Midazolam Compared to IV Diazepam**
2. **Buccal Midazolam Compared to Rectal Diazepam**
3. **Intranasal Midazolam Compared to Rectal Diazepam**
4. **Intramuscular Midazolam Compared to IV Diazepam**
5. **Intramuscular Midazolam Compared to Rectal Diazepam**
6. **Intramuscular Midazolam Compared to Intranasal Midazolam**
7. **Intramuscular Midazolam Comapared to Buccal Midazolam**
8. **Intranasal Midazolam Comapred to Buccal Midazolam**

1. Buccal Midazolam Compared to IV Diazepam:

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does buccal midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) equivalently compared to IV diazepam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does buccal midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to IV diazepam in randomized controlled trials or quasi-randomized trials (or observational or case-control studies) in the prehospital (preferred) or emergency department

GRADE:
Strength of recommendation: weak;
Level of evidence: weak

Evidence:
Limited data suggests that buccal Midazolam at 0.2 mg/kg may be slightly less effective than intravenous diazepam at 0.3 mg/kg for the cessation of seizures in children who are in the emergency department setting. Very limited data suggests that buccal Midazolam is as safe as intravenous diazepam for the treatment of children with seizures who are in the ED setting. However, data is lacking for the pre-hospital setting

Values and preferences were prioritized in order of
- seizure cessation,
- time to seizure cessation,
- respiratory arrest,
- acceptability by prehospital personnel and parents
- ease of use.

See the tables below containing Outcomes A-D for additional information.

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute	Quality	Importance
Outcome A - Seizure cessation (within 5 minutes)												
1 Talukdar 2008		Serious(-1) Serious (-1)		Yes (-1) Yes (-1) ED based	Yes(-1) Yes (-1)		51/60 (85%) GTC only 88.9%	56/60 (93.3%) GTC only 90.2%		8.3% 1.3%	GRADE WEAK LOE - weak	
Outcome B – Time to seizure cessation (from arrival in ED)												
1 Talukdar 2008		Serious (-1)		Yes (-1) ED based	Yes (-1)		2.4 min	3.0 min		0.6 min	GRADE Weak LOE-weak	
Outcome C– Respiratory arrest												
1 Talukdar 2008		Serious (-1)		Yes (-1) ED based	Yes (-1)		0/60 - unclear	0/60 - unclear			GRADE Very weak LOE - weak	
Outcome D – Respiratory depression												
1 Talukdar 2008		Serious (-1)		Yes (-1) ED based	Yes (-1)		0/60 - unclear	0/60 - unclear			GRADE Very Weak LOE - weak	

LOE= Level of Evidence

2. Buccal Midazolam Compared to Rectal Diazepam:

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does buccal midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) more frequently compared to rectal diazepam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) setting or emergency department.

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does buccal midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to rectal diazepam in randomized controlled trials or quasi-randomized trials (or observational or case-control studies) in the prehospital setting (preferred) or emergency department.

GRADE:
Strength of recommendation: strong; Level of evidence: moderate

Evidence:
Literature suggests that buccal Midazolam is more effective than rectal diazepam for the cessation of seizures in children who are in the emergency department setting. Limited data suggests that buccal Midazolam is as safe as rectal diazepam for children with seizures in the emergency department setting. However, data is lacking for the prehospital setting

Values and preferences were prioritized in order of seizure cessation, time to seizure cessation, respiratory arrest, acceptability by prehospital personnel and parents and ease of use. See the tables below containing Outcomes A-E for additional information.

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Buccal	Control	Relative (95% CI)	Absolute	Quality	Importance
Outcome A - Seizure cessation (within 10 minutes)												
3	RCTs	Serious (-1)	No problems (for 2 of higher quality)	(-1)	No (qualitative combining)	Strong Association (+1)					GRADE-MOD	
MacIntyre (2005)	RCT	Serious (-1)		(-1) not prehosp, long sz prior to ED	Not really (even at low end of CI, clear advantage)		109 92 (only 1st episode	110 85 (only 1st episode)	Adj OR 4.1 (2.2-7.6) favoring buccal	24% (11,37) 18%(4,33)	LOE Mod	
Mpimbaza (2008)	RCT	No (not seemingly serious)		(-1) not prehosp, long sz prior, majority with malaria	Not really		165 49 (no malaria)	165 59 (no malaria)	RR 1.42 (1.06-1.90) favors buccal 2.11 (1.26, 3.54)	4.0% 29.4%	LOE Strong	
Baysun (2005)	RCT	Very serious (-2)		(-1) not prehosp, likely long sz prior to ED	Yes		23	20		-7% favors rectal	LOE Weak	

LOE= Level of Evidence

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome B – Time to seizure cessation												
3	RCTs	Serious (-1)	(-1) 2 higher quality RCTs differ	(-1)	Yes (qualitative combining)						GRADE - LOW	
MacIntyre (2005)	RCT	Serious (-1)		(-1) not prehosp, long sz prior to ED	Yes		109 8min (5-20) 92 (only 1st episode) 10 min	110 15min(5-31) 85(only 1st episode) 15 min		7 min favors buccal 5 min	LOE Mod	
Mpimbaza (2008)	RCT	No		(-1) not prehosp, long sz prior, majority with malaria	Yes		114 4.35 min (of those who stopped in <10 min) – median	125 4.75 min (of those who stopped in <10 min) – median		-0.4 min favoring rectal (but only if stopped w/in 10 min)	LOE Strong	
Baysun (2005)	RCT	Very serious (-2)		(-1) not prehosp	Yes		18 (of those who stopped in <10 min	17 (of those who stopped in <10 min		1.4% favoring buccal (diff in those stopping in <5 min)	LOE Weak	

LOE= Level of Evidence

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome C – Seizure recurrence within 1 hour												
2	RCT	Serious (-1)	No problem	(-1)	No (qualitative combining)	Strong Association (+1)					GRADE-MOD	
Macintyre (2005)	RCT	Serious (-1)		(-1) not prehosp, long sz prior to ED	Yes		109 14% 92 (only 1st episode) 13%	110 33% 85 (only 1st episode) 34%		19% (4,36) favors buccal 22% (4, 40)	LOE Mod	
Mpimbaza (2008)	RCT	No		(-1) not prehosp, long sz prior, majority with malaria	Yes		114 (of those who stopped in <10 min) – median	125 (of those who stopped in <10 min) – median		9.5% (favors buccal	LOE Strong	

LOE= Level of Evidence

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome D – Respiratory arrest												
2	RCTs	Serious (-1)	No problems	(-1)	Yes						GRADE-LOW	
MacIntyre (2005)	RCT	Serious (-1)		(-1) not prehosp, long sz prior to ED	Yes		109 (2 arrests, 1.8%)	110 (3 arrests, 2.7%)		0.9%	LOE Mod	
Mpimbaza (2008)	RCT	No		(-1) not prehosp, long sz prior, majority with malaria	Yes		165	165	Unclear (see resp dep)	Unclear	LOE Strong	
Outcome E – Respiratory depression												
2	RCTs	Serious (-1)	No problems	(-1)	Yes						GRADE-LOW	
MacIntyre (2005)	RCT	Serious (-1)		(-1) not prehosp, long sz prior to ED	Yes		109 5% 92 (only 1st episode) 4%	110 6% 85 (only 1st episode) 7%		2%(-4,8) 3%(-4,10)	LOE Mod	
Mpimbaza (2008)	RCT	No		(-1) not prehosp, long sz prior, majority with malaria	Yes		165	165	1 (unclear if any arrest vs low sat)	0 (1.2% each group)	LOE Strong	

LOE= Level of Evidence

3. Intranasal Midazolam Compared to Rectal Diazepam:

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intranasal midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) more frequently compared to rectal diazepam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intranasal midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to rectal diazepam in randomized controlled trials or quasi-randomized trials (or observational or case-control studies) in the prehospital (preferred) or emergency department

GRADE:
Strength of recommendation: weak; Level of evidence: very weak

Evidence:
Very limited data suggests that intranasal Midazolam is at least as effective, and potentially more effective, than rectal diazepam for the cessation of seizures in children who are in the emergency department setting. Very limited data suggests that intranasal Midazolam is as safe as rectal diazepam for the treatment of children with seizures who are in the ED setting. However, data is lacking for the pre-hospital setting.

Values and preferences were prioritized in order of seizure cessation, time to seizure cessation, respiratory arrest, acceptability by prehospital personnel and parents and ease of use. See the tables below containing Outcomes A-E for additional information.

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Intranasal	Control	Relative (95% CI)	Absolute	Quality	Importance
Outcome A - Seizure cessation (within 10 minutes)												
2											GRADE Very low	
Bhattacharyya (2006)	RCT	(-2), including multiple episodes per patient		(-2) Outpt and ED, 37% gen T-C	(-1)		92 episodes (not pts) 96.7%	96 episodes (not pts) 88.5%		8.2% favors intranasal	LOE Very weak	
Fisgin (2002)	RCT	(-2)		(-1) ED	(-1)		23 (87%)	22 (60%)		27%	LOE Weak	
Outcome B – Time to seizure cessation												
2											GRADE Very Low	
Bhattacharyya (2006)	RCT	(-2), including multiple episodes per patient		(-2) Outpt and ED, 37% gen T-C	(-1)		92 episodes (not pts) 178 sec SD 179	96 episodes (not pts) 116 sec SD 127		62 sec	LOE Very weak	
Fisgin (2002)	RCT	(-2)		(-1) ED	(-1)		23 83% <5 min	22 54.5% <5min			LOE Weak	

LOE= Level of Evidence

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome C – Seizure recurrence within 1 hour												
1 Bhattacharyya (2006)	RCT	(-2), including multiple episodes per patient		(-2) Outpt and ED, 37% gen T-C	(-1)		92 episodes (not pts) 3%	96 episodes (not pts) 6.25%		3.25% (favors IN midaz)	GRADE Very Low LOE Very weak	

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome D – Respiratory arrest												
2											GRADE Very Low	
Bhattacharyya (2006)	RCT	(-2), including multiple episodes per patient		(-2) Outpt and ED, 37% gen T-C	(-1)		92 episodes (not pts) 0-unclear	96 episodes (not pts) 0-unclear		0	LOE Very weak	
Fisgin (2002)	RCT	(-2)		(-1) ED	(-1)		23 0-unclear	22 0-unclear		0-unclear	LOE Weak	
Outcome E – Respiratory depression												
1 Bhattacharyya (2006)	RCT	(-2), including multiple episodes per patient		(-2) Outpt and ED, 37% gen T-C	(-1)		92 episodes (not pts)	96 episodes (not pts)		Unclear	GRADE Very Low LOE Very weak	

LOE= Level of Evidence

4. Intramuscular Midazolam Compared to IV Diazepam:

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does IM midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) equivalently compared to IV diazepam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department.

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intramuscular midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to IV diazepam in randomized controlled trials or quasi-randomized trials (or observational or case-control studies) in the prehospital (preferred) or emergency department

GRADE:
Strength of recommendation: weak; Level of evidence: very weak

Evidence:
Very limited data suggests that intramuscular Midazolam is as effective as intravenous diazepam for the cessation of seizures in children who are in the emergency department setting. Very limited data suggests that intramuscular Midazolam is as safe as intravenous diazepam for the treatment of children with seizures who are in the emergency department setting. However, data are lacking for the pre-hospital setting

Values and preferences were prioritized in order of seizure cessation, time to seizure cessation, respiratory arrest, acceptability by prehospital personnel and parents and ease of use. See the tables below containing Outcomes A-E for additional information.

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention IM	Control	Relative (95% CI)	Absolute	Quality	Importance
Outcome A - Seizure cessation (within 10 minutes)												
2		Serious(-1)	No	Yes (-1)	Yes(-1)						**GRADE VERY WEAK**	
Chamber-lain (1997)	RCT	Serious (-1)		Yes(-1) not prehosp, long sz prior to treatment	Yes (-1)		13 (92.3%)	11 (91%)	RR 0.85, (95% CI 0.06, 12.01)	1.3% favors IM	LOE Mod	
Shah (2005)	RCT	Very serious (-2)		Yes (-2), ED, admitted and PICU, severe underlying diseases	Yes (-1)		50 90%	31 93.5% Only those w/o IV initially		-3.5%(favors diazepam)	LOE Very weak	

LOE= Level of Evidence

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative	Absolute	Quality	Importance
Outcome B – Time to seizure cessation if no IV line												
2											GRADE VERY WEAK	
Chamberlain (1997)	RCT	Serious (-1)		Yes(-1) not prehosp, long sz prior to treatment	Yes (-1)		13 7.8 min (time to cessation after ED arrival)	11 11.2 min (time to cessation after ED arrival)		3.3 min (favors IM, includes time to put in IV)	LOE Mod	
Shah (2005)	RCT	Very serious (-2)		Yes (-2), ED, admitted and PICU, severe underlying diseases	Yes (-1)		50 97 sec	31 250 sec		153 sec (2.6 min)-includes time to place IV	LOE Very weak	
Outcome C – Seizure recurrence within 1 hour												
1											GRADE VERY WEAK	
Chamberlain (1997)	RCT	Serious (-1)		Yes(-1) not prehosp, long sz prior to treatment	Yes (-1)		13 30.7%	11 36.4%		-5.4% (favors IM midaz)	LOE Mod	

Outcome D – Respiratory arrest												
2											GRADE VERY WEAK	
Chamberlain (1997)	RCT	Serious (-1)		Yes(-1) not prehosp, long sz prior to treatment	Yes (-1)		13 (92.3%)	11 (91%)	RR 0.85, (95% CI 0.06, 12.01)	1.3%	LOE Mod	
Shah (2005)	RCT	Very serious (-2)		Yes (-2), ED, admitted and PICU, severe underlying diseases	Yes (-1)		50 0/50	31 0/31		0	LOE Very weak	
Outcome E – Respiratory depression												
1											GRADE VERY WEAK	
Chamberlain (1997)	RCT	Serious (-1)		Yes(-1) not prehosp, long sz prior to treatment	Yes (-1)		13	11	Unclear	Unclear	LOE Mod	

LOE= Level of Evidence

5. Intramuscular Midazolam Compared to Rectal Diazepam

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intramuscular (IM) midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) more frequently than rectal diazepam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department.

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intramuscular midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to rectal diazepam in randomized controlled trials or quasi-randomized trials (or observational or case-control studies) in the prehospital (preferred) or emergency department

Evidence:
No literature included in final pool.
No useful comparative data exist on which to recommend or not recommend IM midazolam compared to rectal diazepam for patients < 18 years of age with acute seizures in the prehospital setting.

6. Intramuscular Midazolam Compared to Intranasal Midazolam

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does IM midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) equivalently to intranasal midazolam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does IM midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to intranasal midazolam in randomized controlled trials, quasi-randomized trials, observational or case-control studies in the prehospital (preferred) or emergency department

Evidence:
No literature included in final pool.
No useful comparative data exist on which to recommend or not recommend IM midazolam compared to intranasal midazolam for patients < 18 years of age with acute seizures in the prehospital setting.

7. Intramuscular Midazolam Comapared to Buccal Midazolam

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does IM midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) equivalently to buccal midazolam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does IM midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to buccal midazolam in randomized controlled trials, quasi-randomized trials, observational or case-control studies in the prehospital (preferred) or emergency department

Evidence:
No literature included in final pool.
No useful comparative data exist on which to recommend or not recommend IM midazolam compared to buccal midazolam for patients < 18 years of age with acute seizures in the prehospital setting.

8. Intranasal Midazolam Comapred to Buccal Midazolam

PICO Question:
(Efficacy)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intranasal midazolam lead to seizure cessation (secondary outcomes: time to cessation, recurrence in 1 hour) equivalently to buccal midazolam in randomized controlled trials or quasi-randomized trials performed in the prehospital (preferred) or emergency department

(Safety)
In patients < 18 years of age, with or without a prior a prior history of epilepsy, with an acute tonic-clonic seizure (including those in status epilepticus), does intranasal midazolam have equivalent likelihood of respiratory arrest (secondary outcomes: any respiratory depression, other severe events) compared to buccal midazolam in randomized controlled trials, quasi-randomized trials, observational or case-control studies in the prehospital (preferred) or emergency department

Evidence:
No useful comparative data exist on which to recommend or not recommend Intranasal midazolam compared to buccal midazolam for patients < 18 years of age with acute seizures in the prehospital setting.

Administer 2nd Dose (IV/IO or alternate route) IV diazepam

If short (<=5 mins) transport time, use alternative routes:
Strong recommendation, Low evidence
Values/Preferences:

- Skill competency of EMS provider

Administer second dose of lorazepm or midazolam:
Weak Recommendation , Low Evidence,
Values/Prefeences:

- Seizure cessation in field
- Prompt transfer of child
- Avoid respiratory distress
- Acceptability by prehospital personnel
- Ease of use of therapies in prehospital setting
- Simplicity of algorithim
- Continuum of care between EMS and ED

IV diazepam or lorazepam:
Weak recommendation, Low evidence
Values/Preferences:

- seizure cessation
- respiratory depression

Use of IV Midazolam:
Weak recommendation, Very low evidence
Values/Preferences:

- need to only carry one benzo
- low risk respiratory depression