Appendix 3 GRADE summary of findings

Goal-directed therapy compared to control for sepsis
Patient or population: Adult Patients with Sepsis
Intervention: Early Goal-Directed Therapy
Comparison: Control

28-day mortality											
Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	28-day mortality	placebo	Relative (95% CI)	Absolute (95% CI)	
5	randomised trials	not serious [1]	serious [2]	serious [3,4]	serious [5]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [6]	442/2143 (20.6%)	487/2153 (22.6%)	**RR 0.86** (0.69 to 1.06)	32 fewer per 1000 (from 14 more to 70 fewer)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6]
								24.5%		34 fewer per 1000 (from 15 more to 76 fewer)	

MD – mean difference, RR – relative risk

1. Lack of blinding in all included studies except Rivers et al study
2. Moderate heterogeneity (I2 =71%) was found
3. Different Protocols between control groups were found
4. High differences of mortality between Rivers and harmonized trials were found
5. RR with 95% CI for total trail was 0.86(0.69,1.06). So the largest portion of the meta analysis favor EGDT
6. The publication bias was not assessed because of the limit of the amount of included studies

60-day mortality											
Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	60-day mortality	placebo	Relative (95% CI)	Absolute (95% CI)	
4	randomised trials	not serious [1]	not serious	serious [2,3]	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [4]	450/1986 (22.7%)	473/2011 (23.5%)	**RR 0.94** (0.81 to 1.10)	14 fewer per 1000 (from 24 more to 45 fewer)	⨁⨁⨁◯ MODERATE [1,2,3,4]
								23.6%		14 fewer per 1000 (from 24 more to 45 fewer)	

MD – mean difference, RR – relative risk

1. Lack of blinding in all included studies except Rivers et al study
2. Different Protocols between control groups were found.
3. High differences of mortality between Rivers and harmonized trials were found.
4. The publication bias was not assessed because of the limit of the amount of included studies

90-day mortality											
Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	90-day mortality	placebo	Relative (95% CI)	Absolute (95% CI)	
3	randomised trials	not serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	460/1820 (25.3%)	470/1828 (25.7%)	**RR 0.98** (0.88 to 1.10)	5 fewer per 1000 (from 26 more to 31 fewer)	⨁⨁⨁◯ MODERATE [1,2]
								29.2%		6 fewer per 1000 (from 29 more to 35 fewer)	

MD – mean difference, RR – relative risk

1. Lack of blinding in the three included studies because of the nature of the intervention,
2. The publication bias was not assessed because of the limit of the amount of included studies