

Efficacy and Safety of Oral Micronized Progesterone That Converts to Allopregnanolone as an Adjunctive Treatment in Refractory Status Epilepticus: A Prospective Interventional Phase IIa Study

Pasiri Sithinamsuwan (✉ pasiripmk@gmail.com)

Phramongkutklao hospital and medical college <https://orcid.org/0000-0002-4621-6953>

Wichai Santimaleeworagun

Silpakorn University - Sanam Chandra Palace Campus

Weerayuth Saelim

Silpakorn University - Sanam Chandra Palace Campus

Sippanont Samchai

Phramongkutklao College of Medicine

Puntawat Ruttanajirudorn

Phramongkutklao College of Medicine

Marisa Senngam

Burapha University

Wisithipong Onsombat

Burapha University

Juthathip Suphanklang

Silpakorn University - Sanam Chandra Palace Campus

Research article

Keywords: Epilepsy, Neurosteroids, Refractory status epilepticus, RSE, Progesterone, Allopregnanolone

Posted Date: September 22nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-71483/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: We aimed to study the efficacy and safety of allopregnanolone which convert from oral micronized progesterone as an adjunctive treatment for Thai patients with refractory status epilepticus.

Methods: Adults 18–80 years old who diagnosed with either convulsive or non-convulsive refractory status epilepticus receiving standard AED treatment, intravenous midazolam, for longer than 60 minutes were included. The intervention group received Utrogestan[®] (micronized progesterone, 200 mg/capsule) via enteric feeding every 8 h for five days. Treatments for RSE were continuing along the clinical trial period. Serum allopregnanolone levels were measured by radioimmunoassay (DetectX[®] Allopregnanolone Immunoassay Kit; Arbor Assays, Michigan, United States). Control patients were randomly selected from our hospital RSE cohort during 2015–2019. Continuous data were presented as the mean and standard deviation. Discrete data were assessed by number and percentage. The changes in laboratories were analyzed by paired t-test. The difference between groups were compared by independent sample t-test. The Mann-Whitney U test, Chi-square test or Fisher's exact test were used for non-parametric parameters. A p -value < 0.05 indicated statistical significance. All analyses were performed using SPSS version 26 software (IBM Corp., Armonk, NY).

Results: The average duration of refractory status epilepticus after treatment with midazolam plus progesterone (intervention group) and without progesterone until status epilepticus termination was 25.5 and 58.4 hours, ($p = 0.004$), indicated that allopregnanolone significantly shortens the refractory status epilepticus duration *in vivo*.

Conclusions: Allopregnanolone, produced from oral micronized progesterone, demonstrates efficacy and safety in treating refractory status epilepticus as an adjunctive treatment.

Trial registration: This trial was registered in Thai Clinical Trials Registry (TCTR) database. The trial registration number was "TCTR20200717002", 16 July 2020, retrospectively registered.

Background

Several antiepileptic drugs (AEDs) are required for the treatment of refractory status epilepticus (RSE), especially when anesthetic agents are indicated as a third-line treatment for this condition. Anesthetic agents may cause significant side effects including hypotension, cardiac arrhythmias, prolonged intubation, long intensive care unit (ICU) stay, and increased mortality rate [1, 2]. The mortality rate of adult status epilepticus (SE) in Thailand is approximately 14.5–35%. Meanwhile, the mortality rate of RSE is around 42% [3–6].

Allopregnanolone, a reduced progesterone metabolite and a positive allosteric modulator of γ -aminobutyric acid type A (GABA_A) receptor-mediated conduction, can reduce neuronal excitabilities and increase seizure thresholds, thus yielding a reduction of epileptiform discharges [7, 8]. Previous clinical studies showed that both oral and parenteral forms of progesterone can improve seizure control as well

as suppress seizure discharges in electroencephalography (EEG) [9, 10]. These studies indicate that progesterone contains antiepileptic properties. Some studies using oral allopregnanolone in combination with other AEDs improved seizure control among women with catamenial epilepsies [11]. Few studies are reporting the use of intravenous allopregnanolone in pediatric and adult patients with RSE as an adjunctive treatment is beneficial [12, 13]. Moreover, allopregnanolone was proposed as a safe medication. Allopregnanolone, a so-called "neurosteroid", is not available in Thailand. Nevertheless, micronized progesterone may be administered via an enteric or suppository route and be converted to allopregnanolone *in vivo*. Micronized progesterone is accessible in our country since it is widely prescribed by physicians for treating various obstetric and gynecological conditions. The micronized progesterone exhibits a higher bioavailability and more sustainability than other progesterone formulations and converts to allopregnanolone *in vivo*. We aimed to study the efficacy and safety of allopregnanolone as an adjunctive treatment for Thai patients with RSE. Also, we assessed the bioavailability of allopregnanolone that was converted from oral micronized progesterone among this patient population. Here, we determined the efficacy and safety of oral micronized progesterone for converting to allopregnanolone (an inhibitory neurosteroid) in treating Thai RSE patients as an adjunctive treatment.

In this study we use the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines to described quality of study. The completed CONSORT checklist was described elsewhere.

Methods

Study design and patient population

This study was a Phase IIa prospective open-label interventional study that occurred from January 1st to December 31st, 2019. The study took place within the ICUs of Phramongkutklao Hospital in Bangkok, Thailand.

The inclusion criteria of patients were as follows: (1) Adults, age 18–80 years old. (2) Diagnosed with either convulsive or non-convulsive RSE. (3) Receiving standard AED treatment, including intravenous midazolam, for longer than 60 minutes.

The exclusion criteria of patients were as follows: (1) Pregnancy or lactation. (2) Serious medical problems; renal failure on dialysis, metastatic cancer, active thromboembolism, active bleeding, elevated transaminase enzymes \geq five times of normal value (> 160 U/L), blood pressure lower than 80/50 mmHg. (3) Absolute NPO (as the studied drug was an enteric tubal formulation). (4) Receiving drugs with potential major interaction with progesterone (e.g. estrogen, edoxaban, and venetoclax).

Study protocol

This study was a prospective interventional study. Patients in the intervention group (six patients diagnosed with RSE on intravenous midazolam infusion) received **Utrogestran® (micronized**

progesterone, 200 mg/capsule) via enteric feeding every 8 h for five days (Figure 1). Each dose was combined with 10 ml of olive oil, which acted as a vehicle to carry the agent through the nasogastric tube. Treatments for RSE, as standard guidelines using EEG as guidance, were continuing along the clinical trial period [14].

Serum allopregnanolone levels were measured by radioimmunoassay (DetectX® Allopregnanolone Immunoassay Kit; Arbor Assays, Michigan, United States). The serum allopregnanolone levels were assessed seven times for another pharmacokinetics study.

The six patients in the control group received standard treatment and midazolam infusion for their RSE and were demographically matched with the intervention group. Control patients were randomly selected from our hospital RSE cohort during 2015–2019.

Outcomes measurements

Primary outcomes

- Duration of the first RSE termination, indicated by EEGs for five days
 - EEG SE termination based on burst suppression, background suppression, periodic epileptiform discharges with a frequency < 0.5 Hz[15]

Secondary outcomes

- Duration of the hospital and ICU stays
- Mortality rate and in-hospital mortality rate compared with RSE control patients
- The total dose of midazolam used until the initial termination of RSE termination or until five days elapsed
- Safety (adverse events)
 - Vital signs, clinical adverse events (i.e. rashes, jaundice, hypotension)
 - Abnormal laboratory values: complete blood count, liver function test, creatinine, coagulation test (before and five days after progesterone administration)

Statistical analyses

Continuous data were presented as the mean, and standard deviation. Discrete data were assessed by number and percentage. The changes in laboratories for safety assessments were analyzed by paired t-test. The difference between groups (progesterone and control) were compared by independent sample t-test. The Mann-Whitney U test, Chi-square test, or Fisher's exact test were used for non-parametric parameters. A p -value < 0.05 indicated statistical significance. All analyses were performed using SPSS version 26 software (IBM Corp., Armonk, NY).

Results

Patient demographics

Six patients received oral micronized progesterone (intervention group), and six patients were assigned to the control group (1:1 ratio). The mean age of patients in the intervention group was 63 years (SD 10.1, range 55–80). The most common etiology of RSE was cerebrovascular disease (2/6 patients, 33.3%). The average duration of SE before recruitment was 7.0 hours (SD 0.84). The three most commonly used AEDs during RSE were 1) levetiracetam (6/6 patients, 100%), 2) phenytoin (5/6 patients, 83%), and 3) valproate (3/6 patients, 50%). Only one patient was previously diagnosed with epilepsy (17%). Five out of six patients (83%) exhibited earlier convulsions (convulsive SE) that turned to non-convulsive SE upon joining the study. No statistically significant differences were found in most demographic characteristics between groups. The Status Epilepticus Severity Score (STESS) [16] was calculated. The intervention group demonstrated a relatively higher average STESS value, indicating more severe symptoms compared to the control group; however, no statistically significant difference was found (3.83 versus 2.67, $p = 0.143$). The demographic details are shown in Table 1.

Table 1
Baseline demographic characteristics

	Progesterone (n = 6)	Control (n = 6)	<i>p</i>-value
Age-year	63.0 (10.1)	62.3 (5.5)	0.890
Mean (SD)	55–80	55–71	
Range			
Female-no. (%)	2 (33)	3 (50)	0.558
Etiology of RSE-no. (%)	2 (33)	2 (33)	0.849
Stroke	1 (17)	1 (17)	
Autoimmune	1 (17)	1 (17)	
CNS infection	1 (17)	1 (17)	
Trauma	1 (17)	0	
Metabolic	0	1 (17)	
Tumor			
SE duration-hours	7 (0.8)	10.33 (9.0)	0.388
Mean (SD)	5.5–8	1–24	
Range			
STESS score- 0–6 points	3.83 (1.3)	2.67 (2.2)	0.143
Mean (SD)	3–6	2–5	
Range			
AEDs use-no.(%)	5 (83)	6 (100)	0.500
Phenytoin	3 (50)	5 (83)	0.221
Valproate	6 (100)	6 (100)	1.000
Levetiracetam	1 (17)	1 (17)	1.000
Topiramate			
Convulsive seizure type-no. (%)	5 (83)	5 (83)	1.000
Epilepsy history-no. (%)	1 (17)	1 (17)	1.000

Researchers showed that oral micronized progesterone was converted to allopregnanolone *in vivo*. The average baseline (natural endogenous) allopregnanolone level was 584.5 pmol/mL and C_{max} at 4 h was

2,883.3 pmol/mL. At steady state, the average C_{trough} was 2,694.4 pmol/mL, and the average C_{peak} was 3,255.3 pmol/mL.

Clinical outcomes

The average duration of RSE after treatment with midazolam plus progesterone (intervention group) and midazolam without progesterone (control) until SE termination was 25.5 and 58.4 hours, respectively ($p = 0.004$, Table 2). This finding indicated that allopregnanolone significantly shortens the RSE duration *in vivo*.

Table 2
Clinical outcomes of refractory status epilepticus (RSE)

	Progesterone (n = 6) mean (SD)	Control (n = 6) mean (SD)	<i>p-value</i>
Duration of RSE (hour)	25.5 (12.8)	58.4 (17.1)	0.004*
Duration of hospital stay (day)	57.0 (21.8)	58.7 (39.0)	0.929
Duration of ICU stay (day)	28.7 (12.2)	44.5 (42.3)	0.399
Death: no. (%)	2 (33.3)	4 (66.7)	0.513
Total accumulated midazolam use (mg): median [†]	87.5	330.4	0.394 [□]
* p -value < 0.05, [†] Non-parametric data, [□] Mann-Whitney U test			

The average duration of the ICU and hospital stays seems shorter in the progesterone group than the control group (Table 2). The average duration of hospital stay was 57 days for the intervention group and 58.7 days for the control group ($p = 0.929$). The average duration of the ICU stay was 28.7 days for the intervention group and 44.5 days for the control group ($p = 0.399$).

The mortality rate of the intervention group was approximately half of that of the control group (33.3% versus 66.7%, $p = 0.513$). The median value of total accumulated midazolam infusion until SE termination or death within five days was 87.5 mg for the progesterone group, which was lower than 330.4 mg for the control group ($p = 0.394$, Table 2).

No clinical adverse events were present (i.e. rashes, anaphylactic reactions) in either group. No instances of hypotension or cardiac arrhythmias were reported in the intervention group. Meanwhile, 5/6 patients (83.3%) in the control group developed hypotension and required inotropic agents.

Changes in laboratory findings between the baseline and day 5 after administering progesterone were compared in Table 3. Progesterone exhibited no adverse effects on laboratory parameters.

Table 3
Laboratory findings comparing pre- and post-treatments

Laboratory investigations	Baseline	Day 5	<i>p</i> -value
	Mean (SD)	Mean (SD)	
Hematocrit (%)	28.5 (2.5)	28.4 (5.7)	0.970
White cell count (cells/mm ³)	12,040 (3,232)	8,940 (3,402)	0.261
Platelet (cells/mm ³)	351,200 (35,604.8)	352,600 (201,978.5)	0.987
PTT (second)	20.70 (3.11)	26.95 (5.59)	0.495
INR	0.97 (0.01)	1.11 (0.25)	0.577
Creatinine (mg/dL)	0.92 (0.81)	0.93 (0.78)	0.683
Serum Sodium (mmol/L)	140.14 (3.25)	141.32 (5.09)	0.686
Serum Potassium (mmol/L)	3.39 (0.26)	3.72 (0.20)	0.134
Total Bilirubin (mg/dL)	0.41 (0.07)	0.29 (0.07)	0.002*
Direct Bilirubin (mg/dL)	0.26 (0.09)	0.20 (0.05)	0.102
AST (U/L)	79.0 (64.8)	30.3 (20.8)	0.374
ALT (U/L)	86.6 (58.0)	40.3 (37.3)	0.342
ALP (U/L)	149.0 (51.2)	131.3 (76.2)	0.381
INR, international normalized ratio; PTT, partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase, * <i>p</i> -value < 0.05, statistic: paired t-test			

Discussion

Allopregnanolone is one of the so-called neurosteroids. Few neurosteroids, including allopregnanolone, tetrahydrodeoxycorticosterone, and 3-alpha androstenediol, are inhibitory neurosteroids, meaning that they augment GABAergic signaling [17]. Only allopregnanolone showed *in vitro* and *in vivo* efficacy in controlling seizures in women with catamenial epilepsy as well as adult and pediatric RSE patients [9, 10, 13]. Our results show concordant findings with other previous animal and human studies demonstrating that allopregnanolone improves control of seizures. Allopregnanolone showed improvement compared to the SE controls since it significantly shortens the duration of RSE ($p = 0.004$). Also, the researchers noticed that the average ICU stay, hospital stay, and mortality rates were relatively shorter than those of the control group, although no statistically significant differences were present. A lower midazolam dosage was needed among RSE patients using allopregnanolone compared to controls. Moreover, using progesterone treatment in RSE was quite safe, as no reports of adverse events or serious adverse events in a clinical setting or according to the laboratory results occurred. These efficacy and safety findings were concordant with other previous international studies [13, 18]. Although allopregnanolone is not

commercially available in Thailand, we looked at its precursor, progesterone. Natural progesterone exhibits poor gastrointestinal absorption and a short biological half-life [19, 20]. Therefore, other formulations of progesterone, including injectable, oral, and suppository micronized forms, were developed to improve and stabilize plasma levels [21].

This study was the first clinical research study proving the role of an inhibitory neurosteroid in controlling RSE in Thai patients. We used a commercially available prodrug of allopregnanolone (Utrogestan®) in our limited resource setting. However, this study was only a Phase IIa study. Therefore, the authors suggest further studies to improve methodology, namely a multi-center, double-blind study with a longer duration and larger sample size.

Conclusions

Allopregnanolone, an inhibitory neurosteroid that is produced from oral micronized progesterone, demonstrates efficacy and safety in treating RSE as an adjunctive treatment.

List Of Abbreviations

AEDs Antiepileptic drugs

EEG Electroencephalography

GABA_A γ -aminobutyric acid type A

ICU Intensive care unit

NPO nothing per oral

RSE Refractory status epilepticus

SE Status epilepticus

STESS Status Epilepticus Severity Score

TCTR Thai Clinical Trials Registry

Declarations

Ethics approval and consent to participate

All responsible individuals read the information sheet and signed a consent form. This study was approved by the Institutional Review Board, Royal Thai Army, Medical Department (R150h/61).

Consent for publication

“Not applicable”

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Department of Medicine, Phramongkutklao Hospital and Faculty of Pharmacy, Silpakorn University. The funders had no role in study design, data collection or analysis and has no access to patient information. Also, had no role in decision to publish or preparation of the manuscript.

Authors' contributions

The paper was conceived by PS, SS, PR, and JS. The study protocol was created by PS, both WS and JS. SS and PR performed the diagnosis, EEG reading, proper treatment and monitoring. MS and WS performed insight workflow validation by protocol. All authors commented on initial drafts of the manuscript and approved the final manuscript.

Acknowledgements

The authors appreciate and would like to thank the patients and co-workers who participated in this study. The authors would like to thank Enago (www.enago.com) for the English language review.

Authors' information

¹Division of Neurology, Department of Medicine, Phramongkutklao Hospital and Medical College, Bangkok, 10400, Thailand. ²Faculty of Pharmacy, Silpakorn University, Nakornpathom, 73000, Thailand. ³Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, 20131, Thailand. ⁴Silpakorn University Research and development group in Pharmaceutical care (SURP).

References

1. Kowalski RG, Ziai WC, Rees RN, Werner JK Jr, Kim G, Goodwin H, et al. Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. *Crit Care Med*. 2012;40(9):2677–84.
2. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134(Pt 10):2802–18.

3. Tiamkao S, Pranboon S, Thepsuthammarat K, Sawanyawisuth K. Status epilepticus in the elderly patients: A national data study in Thailand. *J Neurol Sci.* 2017;372:501–5.
4. Phabphal K, Geater A, Limapichart K, Sathirapanya P, Setthawatcharawanich S. Adult tonic-clonic convulsive status epilepticus over the last 11 years in a resource-poor country: a tertiary referral centre study from southern Thailand. *Epileptic Disord.* 2013;15(3):255–61.
5. Tiamkao S, Suko P, Mayurasakorn N, Srinagarind Epilepsy Research G. Outcome of status epilepticus in Srinagarind Hospital. *J Med Assoc Thai.* 2010;93(4):420–3.
6. Kantanen AM, Reinikainen M, Parviainen I, Ruokonen E, Ala-Peijari M, Backlund T, et al. Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy Behav.* 2015;49:131–4.
7. Joshi S, Rajasekaran K, Kapur J. GABAergic transmission in temporal lobe epilepsy: the role of neurosteroids. *Exp Neurol.* 2013;244:36–42.
8. Rhodes ME, Harney JP, Frye CA. Gonadal, adrenal, and neuroactive steroids' role in ictal activity. *Brain Res.* 2004;1000(1–2):8–18.
9. Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures. *Neurology.* 1995;45(9):1660–2.
10. Ramanujam B, Arora A, Malhotra V, Dash D, Mehta S, Tripathi M. A case of recurrent status epilepticus and successful management with progesterone. *Epileptic Disord.* 2016;18(1):101–5.
11. Reddy DS, Rogawski MA. Neurosteroid replacement therapy for catamenial epilepsy. *Neurotherapeutics.* 2009;6(2):392–401.
12. Rogawski MA, Loya CM, Reddy K, Zolkowska D, Lossin C. Neuroactive steroids for the treatment of status epilepticus. *Epilepsia.* 2013;54 Suppl 6:93 – 8.
13. Broomall E, Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, et al. Pediatric super-refractory status epilepticus treated with allopregnanolone. *Ann Neurol.* 2014;76(6):911–5.
14. Betjemann JP, Lowenstein DH. Status epilepticus in adults. *Lancet Neurol.* 2015;14(6):615–24.
15. Kaplan PW. EEG criteria for nonconvulsive status epilepticus. *Epilepsia.* 2007;48(Suppl 8):39–41.
16. Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. *Neurology.* 2006;66(11):1736–8.
17. Reddy DS. Neurosteroids: endogenous role in the human brain and therapeutic potentials. *Prog Brain Res.* 2010;186:113–37.
18. Reddy K, Reife R, Cole AJ. SGE-102: a novel therapy for refractory status epilepticus. *Epilepsia.* 2013;54 Suppl 6:81 – 3.
19. Kincl FA, Ciaccio LA, Benagiano G. Increasing oral bioavailability of progesterone by formulation. *J Steroid Biochem.* 1978;9(1):83–4.
20. Lane G, Siddle NC, Ryder TA, Pryse-Davies J, King RJ, Whitehead MI. Dose dependent effects of oral progesterone on the oestrogenised postmenopausal endometrium. *Br Med J (Clin Res Ed).* 1983;287(6401):1241–5.

21. Nillius SJ, Johansson ED. Plasma levels of progesterone after vaginal, rectal, or intramuscular administration of progesterone. Am J Obstet Gynecol. 1971;110(4):470–7.

Figures

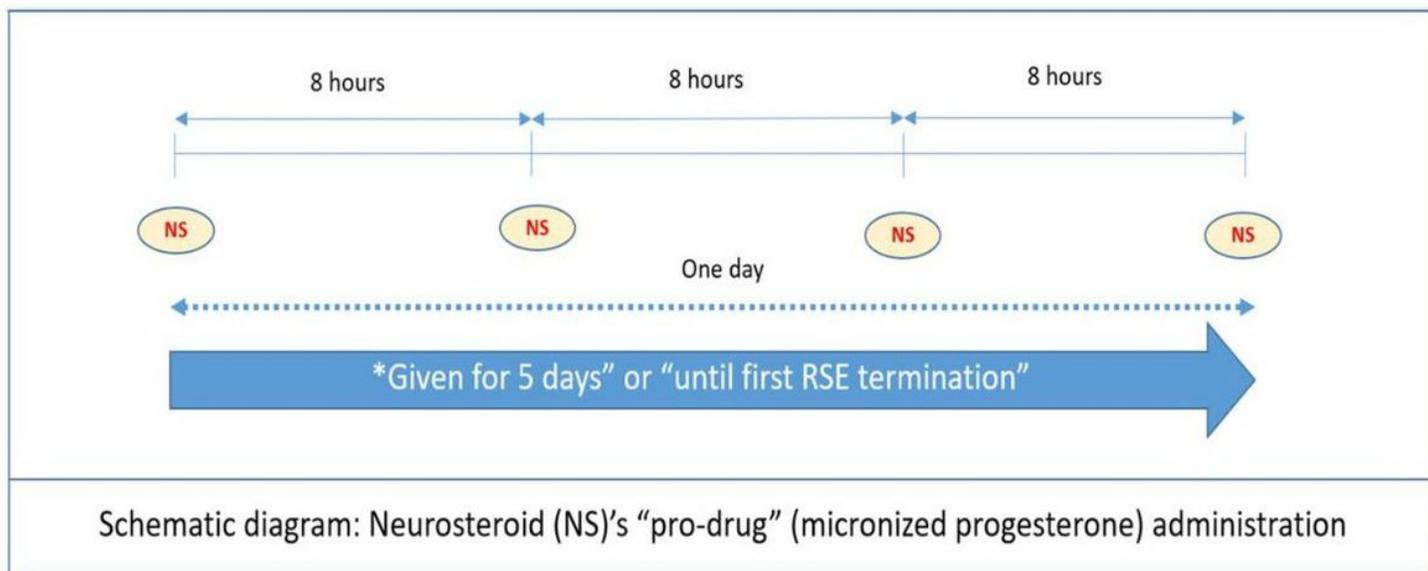


Figure 1

Micronized progesterone administration $t_{1/2}$ of Utrogesten®=8 hours

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORT2010Checklist.doc](#)