To the Editor (In reply),

We thank Wang et al.[1] for their comments on our recent trial[2]. Firstly, we understand that some clinicians do not have access to droperidol. However, the midazolam-olanzapine combination has an efficacy and safety profile very similar to midazolam-droperidol[3] and has potential as a suitable alternative.

Of the 88 patients who received sedative medications prior to the first study medication, 19 were administered pre-hospital intramuscular midazolam according to the paramedic protocol. The median (IQR) dose and time prior to the first study medication was 10 (6-16) mg and 66 (38-125) minutes, respectively. In the emergency department, a total of 105 doses of sedative medication were administered prior to the first study medication: median (IQR) time prior to the first study medication was 48 (23-89) minutes. The large majority were oral doses of diazepam (n=45) or olanzapine (n=36) with median (IQR) doses of 10 (10-10) mg for both medications. The remaining sedative medications included other benzodiazepines, antipsychotics and ketamine, via a range of administration routes.

The use of any oral or parenteral benzodiazepine or neuroleptic (typically oral diazepam or olanzapine in our institutions) prior to enrolment was dichotomized into "yes" or "no" and added into the Cox regression model. This variable had no significant impact on the model. Given the small numbers and variability in medications, doses and timing, no further modelling of pre-enrolment sedation was possible.

We can confirm that the discrepancy between the Trial Registry information and our report was a clerical oversight. We designed the trial to have the most clinically relevant primary outcome i.e. ‘proportion of patients adequately sedated at 10 minutes’. This primary outcome, and the sample size calculation based upon it, was recorded in the study protocol that was approved by our ethics committee before the study began. The term ‘time to sedation’ that we recorded in the Registry was too broad, as it could include both proportions sedated at various time points and actual times to sedation.

The propensity of midazolam (alone or in combination) to cause respiratory events is well known.[2,3] We agree that the risk/benefit of midazolam-droperidol use needs to be weighed. However, while the event rate is important, the consequences of these events also need to be considered. In this regard, the large majority of respiratory events are transient, easily managed and are of no clinical consequence. As Wang et al.[1] suggest, there are confounding variables that impact upon respiratory events. In our study, patients intoxicated with alcohol had more respiratory events than those who did not (18.7% versus 12.1%, respectively). However, patients intoxicated with recreational drugs did not have more respiratory events (14.1% versus 15.5%, respectively). In a multi-centre study, we are currently investigating the impact of sedative

medications, intoxication and other confounding variables on the risk of respiratory (and other) events.

References:

1. Wang JJ, Nguy P, Villeneuve E, Langlois H, Gosselin S. Sedating the agitated patient - a moving target? (Letter to the Editor) *Annals Emerg Med* 2016: TBA

2. Taylor DM, Yap CY, Knott JC, Taylor SE, Phillips GA, Karro J, Chan EW, Kong DC, Castle DJ. Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial. *Annals Emerg Med* 2016 Oct 10.

3. Chan EW, Taylor DMcD, Knott JC, Phillips GA, Castle DJ, Kong DCM. Intravenous droperidol or olanzapine as adjuncts to midazolam for the acutely agitated patient: a multi-centre, randomised, double-blind, placebo-controlled clinical trial. *Annals Emerg Med* 2013;61:72-81