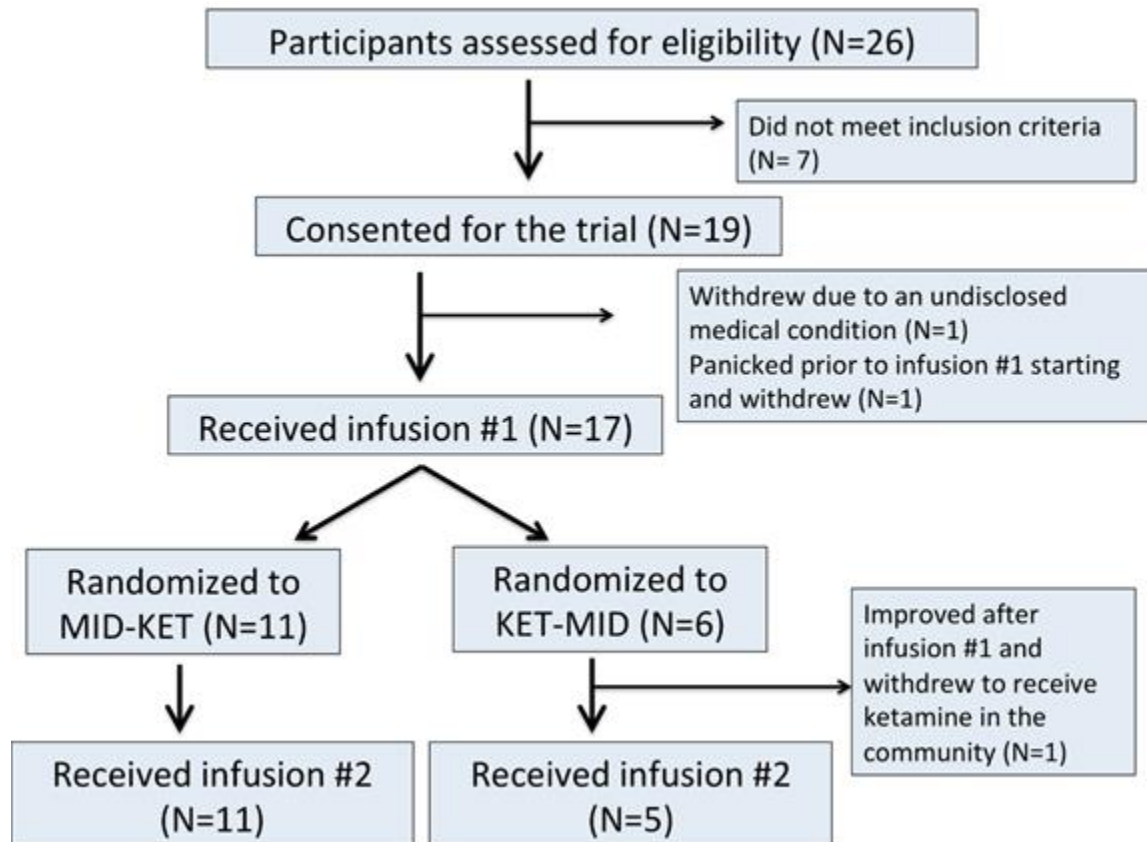Data supplement for Dwyer et al., Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. Am J Psychiatry (doi: 10.1176/appi.ajp.2020.20010018)

CONSORT Patient Flowchart

SUPPLEMENTAL RESULTS

A) Response Analysis
Treatment response was defined *a priori* as a >50% reduction in MADRS score at any assessment conducted by the blinded rater within the three days following infusion. We *a priori* defined response as being present any time between days 1–3 following infusion because adult subjects typically experience their maximum response to ketamine somewhere between 1 to 3 days following initial infusion, we wanted to capture all possible responders (e.g., participants who have an improvement on day 1 that do not meet response criteria, but further improve and meet response criteria on day 2), and to maximize statistical power.

Figure 2B in the main text describes the primary response analysis using the above criteria, although all subjects who met response criteria for either medication did so by day 2 (McNemar χ^2=4.0, df=1, p=0.046). Here, that analysis is supplemented by a response analysis of using only day 1 MADRS data (McNemar χ^2=1.77, df=1, p=0.18, n=17).

| | | **Ketamine** | |
		MADRS D1 or D2 Response	Non-Response
Midazolam	**Response**	5 Both	1 Midazolam only
	Non-Response	8 Ketamine only	3 Neither

| | | **Ketamine** | |
		MADRS D1 Response	Non-Response
Midazolam	**Response**	3 Both	2 Midazolam only
	Non-Response	7 Ketamine only	5 neither

We also examined response as measured by the CDRS-R on Day 1. To calculate response (50% reduction from baseline score), the floor of the CDRS-R was subtracted from all scores (the lowest possible score, if a participant/parent answers the lowest value on all questions, on the CDRS is 17). Three participants were excluded from this analysis due to missing data (McNemar χ^2=6.13, df=1, p=0.013, n=13).

| | | **Ketamine** | |
		CDRS-R D1 Response	Non-Response
Midazolam	**Response**	1 Both	0 Midazolam only
	Non-Response	8 Ketamine only	5 Neither

B) MADRS Period Analysis

Carryover effects—i.e., whether a treatment effect from the first infusion persisted into the second infusion period—were tested by comparing whether the difference in baseline scores between the first and second infusion periods were significantly different based on initial treatment assignment. Period effects—i.e., whether participants differed at the start of the first infusion compared with the second infusion, regardless of treatment assignment—were tested by a paired t-test comparing baseline MADRS scores in the first and second infusion periods regardless of initial treatment assignment. Order or sequence effects (a treatment-by-period interaction) were determined via a log likelihood ratio test by systematically specifying nested models. Both nested models included first-order treatment and period effects. We defined a nesting saturated model with an additional treatment-by-period interaction term and compared it to a nested base model without the interaction term.

Carryover effects were tested by examining the difference between baseline scores in the first and second infusion periods based on whether subjects received midazolam or ketamine first (d=2.32 (95% CI=−10.0, 14.73), t=0.40, df=15, p=0.69). Analysis of period effects showed that subjects demonstrated reduced baseline MADRS scores at the beginning of the second infusion period compared to the beginning of period 1 regardless of initial treatment assignment (d=5.81 (95% CI=0.17, 11.61), t=2.14, df=15, p=0.025). Analysis using the log likelihood ratio test demonstrated no significant order effects (treatment-by-period interaction, p=0.40).