A Prospective 5-Year Re-Examination of Alcohol Response in Heavy Drinkers Progressing in Alcohol Use Disorder

Supplemental Information

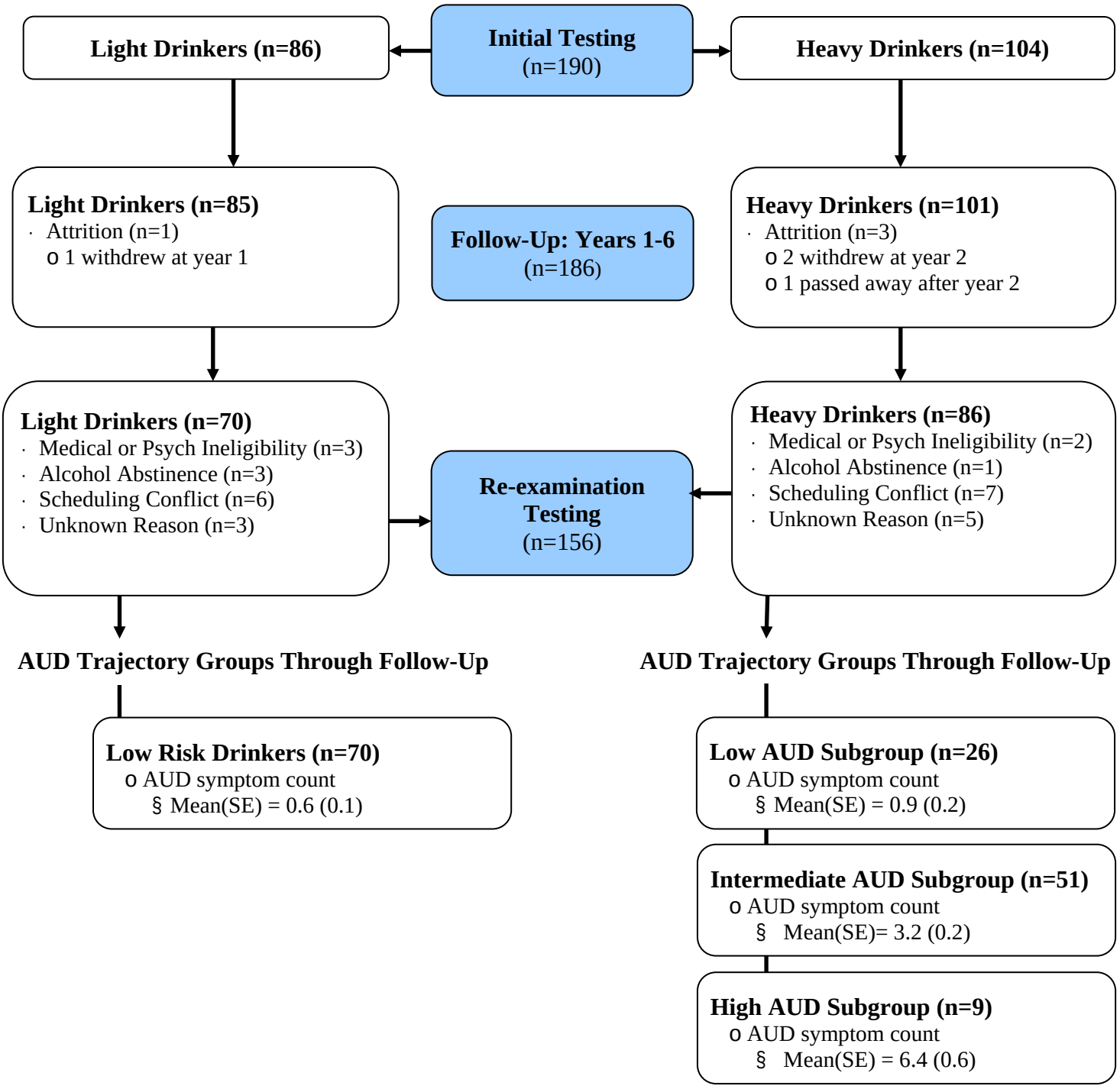


Figure S1. CONSORT Flow Chart of LD and HD Groups at Different Study Phases and AUD Trajectory Groups over Follow-Up

Table S1. Baseline Characteristics of Participants at CSDP Study Enrollment

	Initial Testing		HD AUD Subgroups		
	LD (n = 70)	HD (n = 86)	Low (n = 26)	Intermediate (n = 51)	High (n = 9)
Demographics & Health					
Age (years)	26.1 (0.4)	25.2 (0.3)	25.9 (0.6)	25.0 (0.4)	24.9 (1.2)
Education (years)	16.5 (0.3)	15.7 (0.2) **	15.4 (0.3)	15.9 (0.2)	15.4 (0.9)
Beck Depression Inventory	2.1 (0.3)	2.8 (0.3)	1.8 (0.4)	2.8 (0.4)	5.2 (1.2) **f
Spielberger Trait Anxiety (T-Score)	43.7 (0.9)	45.1 (0.8)	42.9 (1.3)	45.2 (1.0)	50.8 (3.6) *f
Marijuana Use (weekly or more)	0%	10%**	4%	12%	22%
Cigarette Use (weekly or more)[a]	6%	55%***	54%	55%	56%
Stimulant Use (weekly or more)[b]	0%	0%	0%	0%	0%
AST (units/L)[c]	21.94 (0.8)	23.0 (1.2)	25.9 (3.6)	21.9 (0.8)	20.8 (2.3)
ALT (units/L)[c]	21.0 (1.6)	22.1 (2.1)	26.9 (6.2)	19.9 (1.4)	20.9 (4.4)
Average Drinking at Enrollment[d]					
Frequency (days/month)	6.3 (0.4)	14.6 (0.6) ***	13.5 (1.1)	14.7 (0.7)	17.0 (2.6)
Quantity (drinks/drinking day)	1.7 (0.1)	5.4 (0.4) ***	5.6 (1.1)	5.2 (0.3)	5.9 (0.8)
Binge Frequency (days/month)[e]	0.1 (0.1)	7.8 (0.4) ***	6.4 (0.6)	8.3 (0.5)	8.8 (0.5)
Max # Drinks in One Occasion	2.7 (0.1)	10.1 (0.5) ***	9.8 (1.3)	10.1 (0.6)	11.3 (1.5)
AUDIT Total Score	3.2 (0.2)	11.4 (0.4) ***	9.2 (0.5)	12.0 (0.5)	14.7 (0.8) ***g
DrInC-2R Total Score	2.2 (0.3)	14.7 (1.0)***	9.7 (1.5)	15.7 (1.0)	22.9 (5.0) ***g

Data are mean (SEM) or n (%). *p < .05, **p < .01, *** p < .001.

[a] Taken from previous month Timeline Follow-Back Interview for the month proceeding study enrollment.

[b] Stimulant use included both prescription and recreational drugs.

[c] Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) blood tests for liver functioning.

[d] Drink based on standard definition of one drink = 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor, and average values represent values taken from Timeline Follow-Back Interview for the month preceding study enrollment.

[e] Binge defined as ≥5 drinks per occasion for males and ≥4 drinks for females.

[f] High > Intermediate = Low.

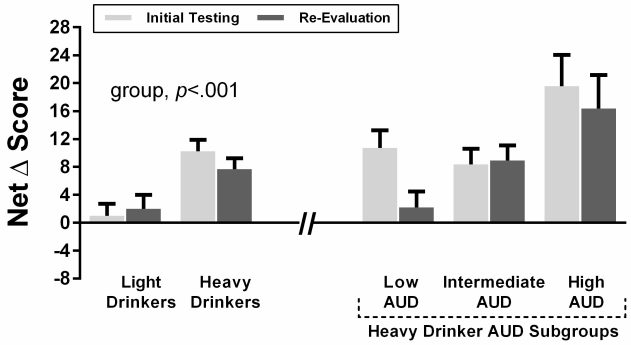
[g] High > Intermediate > Low.

Supplemental Results

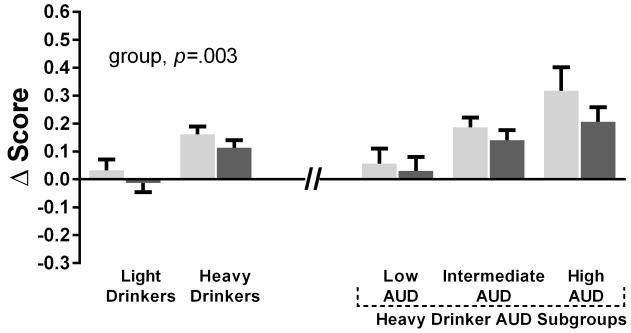
Pearson correlations were conducted on the relationship of stimulation to liking and wanting to examine if the stimulating effects of alcohol were pleasurable. The results at peak BrAC (change and net change scores based on the 60 minute time point) showed that the relationships between stimulation and liking, and stimulation and wanting, were indeed positive for the high AUD group, *r*s = +0.74 ($p < .05$) and +0.41 (p = ns), respectively, at initial testing, and *r*s = +0.47 (p = ns) and +0.71 ($p < .05$), respectively, at re-examination testing. For the intermediate AUD group, the correlations were also positive, *r*s = +0.51 ($p < .001$) and +0.44 ($p = .001$), respectively, at initial testing, and *r*s = +0.38 ($p < .01$) and +0.24 (p = ns), respectively, at re-examination testing. These correlations were non significant in the low AUD group, *r*s = +0.14 (p = ns) and +0.18 (p = ns), respectively, at initial testing, and *r*s = +0.14 (p = ns) and +0.005 (p = ns), respectively, at re-examination testing.

Rising Limb (30 min) Responses

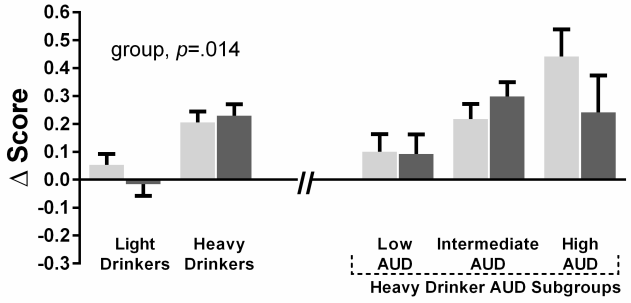
S2A) Stimulation



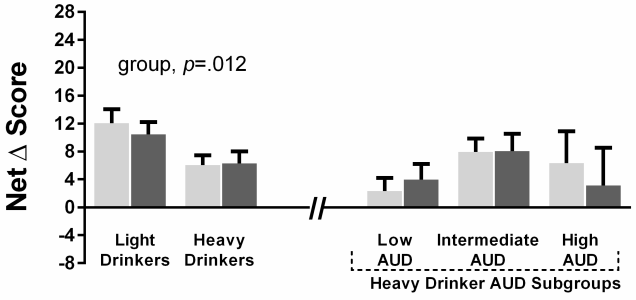
S2B) Like



S2C) Want More

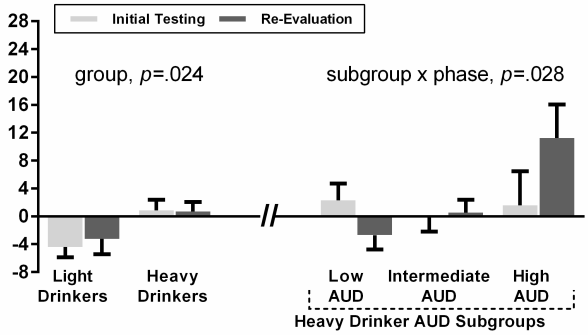


S2D) Sedation

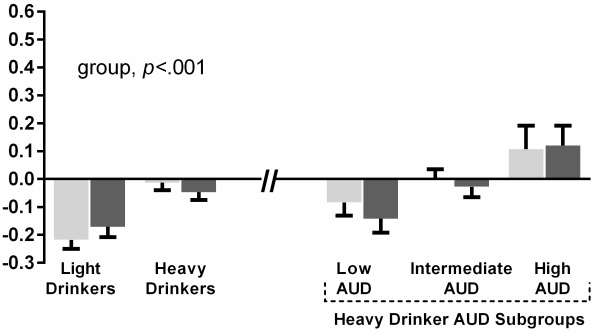


Declining Limb (120 min) Responses

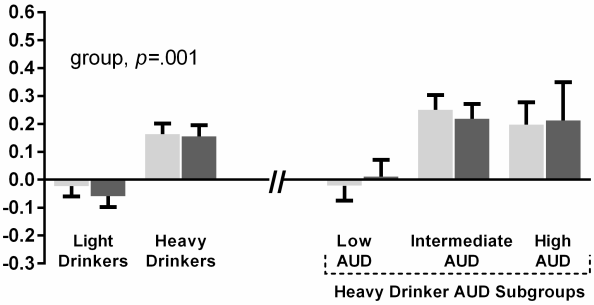
S2E) Stimulation



S2F) Like



S2G) Want More



S2H) Sedation

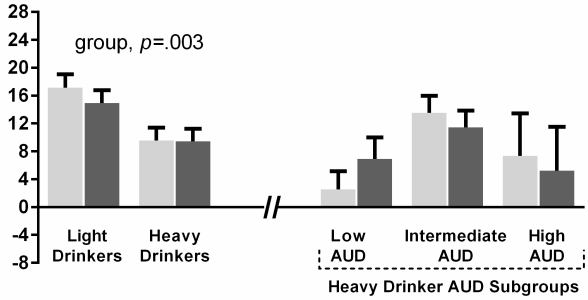


Figure S2. **Alcohol Stimulation, Liking, Wanting, and Sedation at Rising (+30 min) and Declining (+120 min) Limbs at Both Initial and Re-Examination Phases.** Data are shown for light (*n* = 70) and heavy drinker groups (*n* = 86), as well the heavy drinker AUD trajectory subgroups, including low AUD (*n* = 26), intermediate AUD (*n* = 51), and high AUD (*n* = 9). (**A**) and (**D**) are the net change score during the rising limb (alcohol session +30 min BrAC minus baseline change score minus the same change score for the placebo session) for the BAES stimulation and sedation, respectively; three outliers (<3 SD below mean) were removed in this analysis. (**B**) and (**C**) are the DEQ like and want more change scores (alcohol session +30 min minus placebo session), respectively. Figures on the right side (**E**, **F**, **G**, **H**) are similar scores comprised from the declining limb at +180 minutes. GEE results are depicted for group and group x phase effects; see Tables S2 and S3 for post-estimation testing results.

Table S2. GEE Analysis Summary of Alcohol Responses in Light (LD) and Heavy Drinkers (HD) by Testing Phase and HD AUD Subgroups by Testing Phase from Scores Taken During the Rising (+30 min) BrAC Curve

Time 1 (30 min)

Alcohol Responses	Group (LD vs HD)			Phase			Group x Phase			Post Estimation Group Comparison
	β	SE	*p*	β	SE	*p*	β	SE	*p*	
Stimulation	8.44	2.42	**<0.001**	1.46	2.04	0.474	-2.88	2.76	0.296	HD > LD
Like	10.95	4.42	**0.013**	-3.78	4.10	0.358	0.23	5.51	0.966	HD > LD
Want More	14.01	5.73	**0.014**	-6.37	4.97	0.200	9.63	6.68	0.149	HD > LD
Sedation	-6.06	2.42	**0.012**	-1.56	2.05	0.444	1.85	2.75	0.502	HD < LD
Cortisol	--	--	--	--	--	--	--	--	--	N/A

Alcohol Responses	HD AUD Subgroup			Phase			AUD Subgroup x Phase			Post Estimation Group Comparison
	β	SE	*p*	β	SE	*p*	β	SE	*p*	
Stimulation	4.32	2.01	**0.032**	-1.97	1.95	0.314	5.09	3.00	0.090	High > Intermediate = Low
Like	12.54	4.40	**0.004**	2.40	9.75	0.806	-3.44	5.12	0.502	High = Intermediate > Low
Want More	14.87	6.36	**0.019**	9.66	12.44	0.437	3.54	6.54	0.588	High = Intermediate > Low
Sedation	3.23	2.53	0.201	3.94	5.81	0.498	-2.15	3.05	0.481	N/A
Cortisol	--	--	--	--	--	--	--	--	--	N/A

Results from GEE analyses [coefficient (β), standard error (SE), and *p* value] for alcohol response measures (net change or change scores at rising (+30 min) BrAC) for group (HD vs LD), subgroup (HD AUD Subgroups), phase (initial and re-examination), and their interaction(s). Alcohol responses were net change and change scores from placebo at rising BrAC (+30 min) for each phase.

Table S3. GEE Analysis Summary of Alcohol Responses in Light (LD) and Heavy Drinkers (HD) by Testing Phase and HD AUD Subgroups by Testing Phase from Scores Taken During the Declining (+120 min) BrAC Curve

Time 3 (120 min)

Alcohol Responses	Group (LD vs HD)			Phase			Group x Phase			Post Estimation Group Comparison
	β	SE	*p*	β	SE	*p*	β	SE	*p*	
Stimulation	5.23	2.32	**0.024**	1.21	2.32	0.600	-0.85	3.15	0.788	HD > LD
Like	20.18	4.33	**<0.001**	4.63	3.94	0.240	-7.58	5.33	0.155	HD > LD
Want More	18.19	5.52	**0.001**	-3.55	4.87	0.467	3.30	6.59	0.616	HD > LD
Sedation	-7.79	2.63	**0.003**	-2.16	2.15	0.315	2.38	2.90	0.412	HD < LD
Cortisol	--	--	--	--	--	--	--	--	--	N/A

Alcohol Responses	HD AUD Subgroup			Phase			AUD Subgroup x Phase			Post Estimation Group Comparison
	β	SE	*p*	β	SE	*p*	β	SE	*p*	
Stimulation	-0.90	2.34	0.700	-11.89	5.82	0.041	6.70	3.05	**0.028**	High = Intermediate = Low
Like	9.39	4.36	**0.031**	-10.70	10.86	0.324	3.59	5.68	0.527	High = Intermediate > Low
Want More	15.88	6.24	**0.011**	5.80	14.62	0.692	-3.01	7.64	0.694	High = Intermediate > Low
Sedation	5.16	2.96	0.081	7.35	5.87	0.210	-4.22	3.07	0.168	N/A
Cortisol	--	--	--	--	--	--	--	--	--	N/A

Results from GEE analyses [coefficient (β), standard error (SE), and *p* value] for alcohol response measures (net change or change scores at declining (+120 min) BrAC) for group (HD vs LD), subgroup (HD AUD Subgroups), phase (initial and re-examination), and their interaction(s). Alcohol responses were net change and change scores from placebo at declining (+120 min) BrAC for each phase.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title (*Note: Study is a longitudinal, laboratory based trial)	N/A*
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5, 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6, 7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,7

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	2, 5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9, 10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9, 10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9, Supp Fig S1
	13b	For each group, losses and exclusions after randomisation, together with reasons	9, Supp Fig S1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1, Supp Table S2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9, 10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10, 11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10, 11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14,15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14,15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.