Discrepancies between publication, protocol and registration

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To the Editor:

We noticed divergences between public registrations, protocol versions and the publication of Carhart-Harris et al.¹ The publication lists one primary outcome (changes on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report/QIDS-SR-16) and mentions functional MRI (fMRI) data was collected for treatment response prediction, but not yet analyzed. Two protocol versions (v5- pre-trial and v7- at completion) explicitly declare two primary outcomes, i.e., 6 weeks changes in amygdala BOLD response to emotional faces (using fMRI) and in depression (QIDS-SR-16). Similarly, the three public trial registrations list both outcomes, though with different rankings: in two registries (NCT03429075, ISRCTN10584863) the fMRI outcome is primary and the QIDS-SR-16 secondary, while in another (EudraCT2017-000219-18), the order is reversed. Initially (protocol v1), the study's main purpose was evidencing superiority of a single psilocybin dose over placebo (sub-therapeutic dose). Subsequently, the placebo group was dropped, dosage and treatment duration changed, and the main purpose amended to comparison against escitalopram. Still, sample size calculations remained based on effect estimations anticipated for the placebo comparison. Disclosure and justification of all protocol changes are warranted.

References:

1. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine* 2021;384:1402-11.

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