Supplementary Material

Article Title: Treating Insulin Resistance With Metformin as a Strategy to Improve Clinical Outcomes in Treatment-Resistant Bipolar Depression: A Randomized, Quadruple-Masked, Placebo-Controlled Clinical Trial (the TRIO-BD Study)

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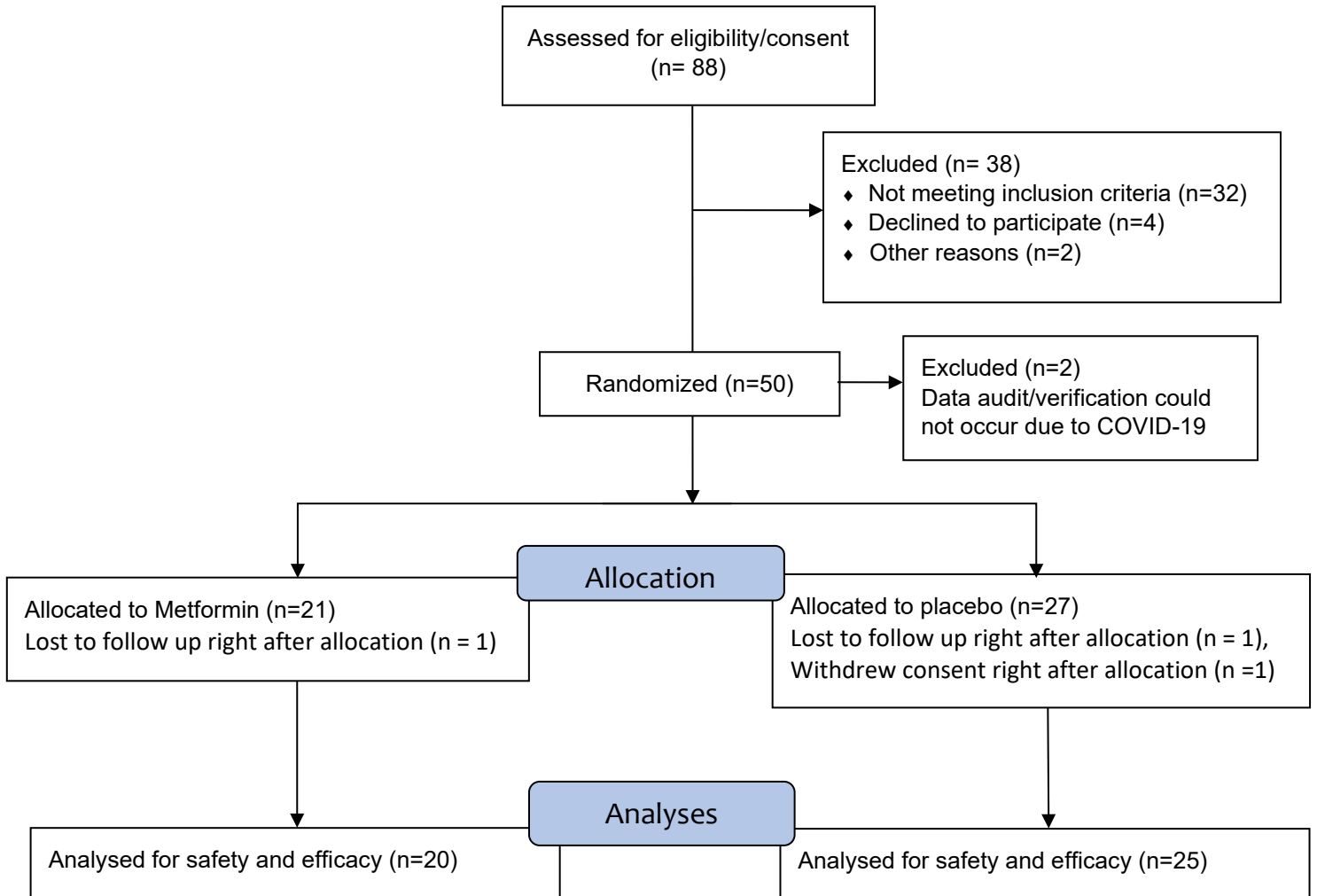## List of Supplementary Material for the article

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Supplementary Figure 1

Consort Figure -Treating Insulin-**R**esistance with Metformin as a strategy to **I**mprove Clinical **O**utcomes in Treatment-Resistant **B**ipolar **D**epression: A Randomized, Quadruple-Masked, Placebo-Controlled Clinical Trial (The **TRIO-BD** Study)

Enrollment of Patients

Assessed for eligibility/consent
(n= 88)

Excluded (n= 38)
- Not meeting inclusion criteria (n=32)
- Declined to participate (n=4)
- Other reasons (n=2)

Randomized (n=50)

Excluded (n=2)
Data audit/verification could not occur due to COVID-19

Allocation

Allocated to Metformin (n=21)
Lost to follow up right after allocation (n = 1)

Allocated to placebo (n=27)
Lost to follow up right after allocation (n = 1),
Withdrew consent right after allocation (n =1)

Analyses

Analysed for safety and efficacy (n=20)

Analysed for safety and efficacy (n=25)

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Supplementary Table 1 - Adverse Events Reported at ≥ 5% in Either Treatment Group					
Adverse Event	Metformin n = 20		Placebo n = 25		p value[*]
	N	%	N	%	
Gastrointestinal Symptoms					
loose stool/diarrhea	8	(40)	8	(32)	0.7551
dry mouth	2	(10)	1	(4)	0.5772
nausea	7	(35)	5	(20)	0.3200
vomiting	2	(10)	3	(12)	1.0000
constipation	0	(0)	4	(16)	0.1174
abdominal discomfort	1	(5)	2	(8)	1.0000
heartburn	1	(5)	3	(12)	0.6174
Neurological Symptoms					
headaches	2	(10)	5	(20)	0.4367
[*] Footnote Fisher Exact Test					

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