The Prospective Incidence of Treatment Resistant Schizophrenia: Analysis of the CATIE Trial using the TRRIP Consensus

1. Supplementary Analysis and Results

1.1 Participants Meeting TRRIP Criteria

Figure S2 shows that at some time point, almost all participants met the moderate impairment threshold for SOF and absolute symptom criteria for TRRIP emphasising the role of rigorously defined symptom response and adequate trial criteria in identifying TRS cases.

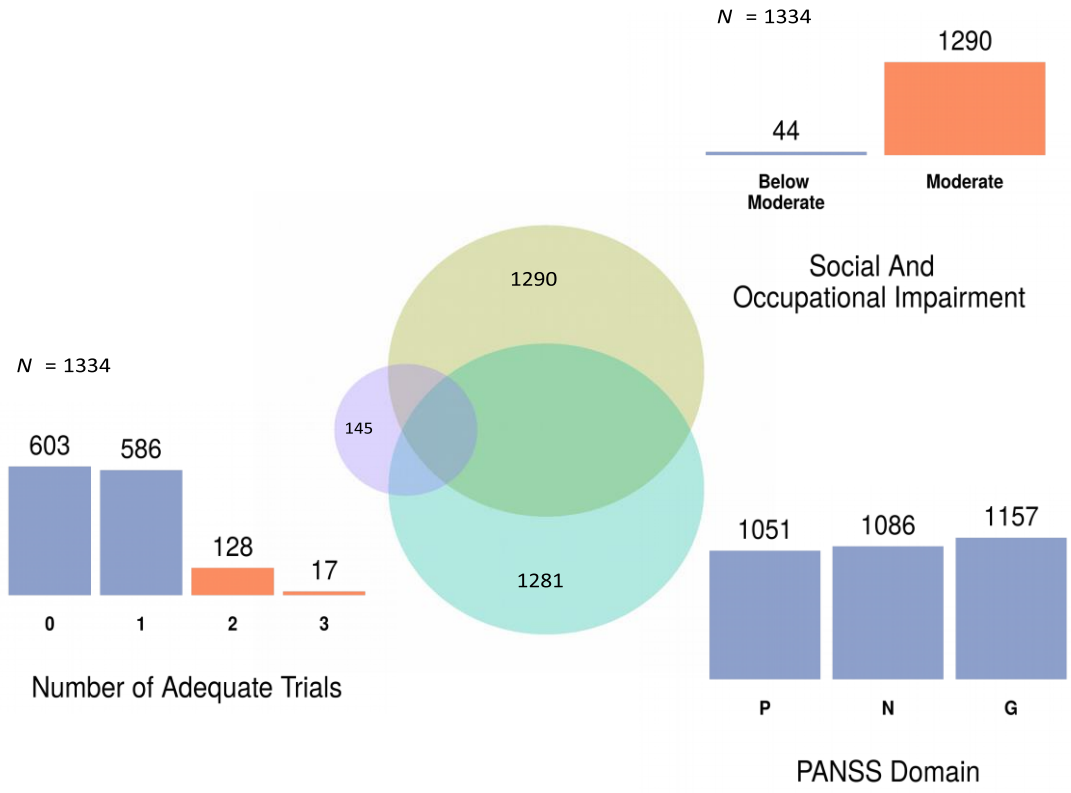

Figure S2: Over the duration of the trial, for each of the three major TRRIP criteria: Social and Occupational Functioning – of 1334 participants, 1290 were at some time scoring moderate (or higher); Number of Adequate Trials – a total of 128 participants had 2 adequate trials, with a further 17 having 3 adequate trials; PANSS Domains (not mutually exclusive) – around 80% of participants were at some point meeting the absolute (but *not* necessarily symptom response) criteria in positive, negative or general domains

1.2 TRS Associations with Baseline Data: Whole Population and AT Sub-Group

For **demographic** variables, in the AT group only (Table 3, main text) increasing age was associated with a small decrease in the probability of developing TRS (Odds Ratio = 0.976) that given the confidence interval (95% CI = [0.953, 0.999]) is unlikely to represent a clinically relevant finding.

Repeating the analysis for psychopathology associating with TRS status in the AT sub-population (Table 3, main text) showed comparable results as for the whole population, but notably, in analyses adjusted for demographics, only PANSS N (OR = 1.062, 95% CI = [1.015,1.11]) and G (OR = 0.950, 95% CI = [0.916,1.74]) and age (OR = 0.974, 95% CI = [0.951,0.998]) were associated with future TRS status. 73 of the 77 TRS cases met the TRRIP absolute symptom criteria at baseline, so these associations are unlikely to be predictive, but rather circular, representing the fact that participants in the AT group who went on to be TRS had high symptom burden at baseline.

1.3 Approximating Crude Incidence Rates from Comparable Literature

For the two most recent population estimates of treatment resistance [1,2], we can estimate a crude incidence rate with some assumptions. For [1], there is no record of treatment resistance- free (TR-free) person-contributed years or recording of when (within the 10-year follow-up window the participants developed TR. From Table One of Demjaha et al. (2017) we can derive:

Total N = 286	Responders	TR at Onset	TR Later
N	212	62	12
Follow-up Years	9.8	0.5	9.3
Years Contributed	$212 \times 9.8 = 2077.6$	$62 \times 0.5 = 31$	$12 \times \frac{9.3}{2} = 55.8$

Where for later onset cases, we assume TR develops at approximately 5 years (i.e. half-way through follow-up) and for TR at onset cases, at least 6 months of non-response was observed. The resulting incidence rate is therefore:

$$100 \times \frac{74}{2077.6 + 31 + 55.8}$$

which equates to approximately 3.4 per 100 person-years. Similarly, for [2], 81 of 240 participants develop TR over a mean of 5.4 years of follow up for all participants: where again, as we have no time to TR events for individual cases, we have assumed that TR develops half-way through follow-up.

Total N = 240	Responders	TR
N	159	81
Follow-up Years	5.4	5.4
Years Contributed	$159 \times 5.4 = 858.6$	$81 \times \frac{5.4}{2} = 218.7$

This yields:

$$100 \times \frac{81}{858.6 + 218.7}$$

which equates to an incidence rate of 7.5 per 100 person-years.

References

1. Demjaha A, Lappin JM, Stahl D, et al. Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychol Med.* 2017;47(11):1981-1989.
2. Lally J, Ajnakina O, Di Forti M, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med.* 2016;46(15):3231-3240.