Box S7 | Significance of placebo effects, gender and culture for CHR subject stratification and clinical trials

Although considerable progress has been made in the study of CHR subjects and trials of putative, preventative treatment, several questions remain to be further investigated within the framework of larger, more highly-powered studies.

First, the influence of placebo remains uncertain and is hard to decipher inasmuch as control groups are never ‘untreated’ per se, but rather benefiting from — at least — routine care (Table 1).

A second issue is cultural and demographic differences.1,2 This is of particular relevance since: 1), migrant status is a risk factor for psychosis; 2), there are inter-country differences in conversion rates, pathways to care and response to antipsychotics and 3); culture and beliefs impact the application of psychological therapies.2,4

Third, schizophrenia reveals sex differences in age of onset, severity, profile of symptoms and response to treatment.4,6,7 Males have a more severe prognosis and the possible shielding role of oestrogen is indicated by 1), a greater risk of psychosis in females during periods of low oestrogen and 2), beneficial effects of oestrogen supplementation in female patients with schizophrenia.4,6,8 For safety reasons, oestrogen is unlikely to be tested in female CHR subjects, yet a sexual dimorphism also exists in the prodromal phase with greater baseline functional deficits in males strongly predictive of conversion.9 While the precise role of gonadal hormones versus genetic factors in gender differences remains to be clarified, these observations — together with experimental work10 — underpin the pertinence of gender to the prediction of conversion, patient sub-classification and clinical trial design.