Supplementary Table 4. Basic concepts of pharmacovigilance

Limitations of the RCT
RCTs are the cornerstone of drug evaluation but are designed to demonstrate efficacy of drugs and not ADRs, the second element of the risk-benefit balance. These shortcomings have been summarized in the so-called "five too's" of RCTs:[66] • include "too few" patients, no more than 1,500 before drug approval; • are "too simple," not including usually polypathological or polymedicated patients, i.e., the main populations later exposed to drugs; • are "too often" concerned with median ages, excluding very young or old subjects. However, subjects over 65−70 years old and beyond are frequently those primarily receiving both old and new medications; • "too narrow," respecting very restrictive and well-defined indications not followed in daily clinical practice; and • are "too brief," including, for example, patients treated for only a few months for a chronic disease.
VigiBase
VigiBase, the WHO's global pharmacovigilance database:[67] • It is located at the Uppsala Monitoring Centre, Uppsala, Sweden. • It currently has >25 million reports of spontaneously reported ADRs from the drug agencies of 145 countries. New reports arrive daily. • ADRs are sometimes classified by the reporting clinician but normally those who report would enter free text information and pharmacovigilance staff at a regional or national center or pharmaceutical company would do the encoding using the categories provided by the database. Each patient can be classified in 1 or several ADR categories. This is particularly true for clozapine ADRs, in the experience of the author.
Comparison of transnational clozapine fatal outcomes in VigiBase
The comparison of transnational fatal outcomes in VigiBase is limited by lack of knowledge of:[68] • ADRs occurring versus those reported, • reports of fatal versus non-fatal outcomes, and • the number of patients taking clozapine corrected by population size. Thus, only "gross" transnational comparisons can be made.

ADR, adverse drug reaction; RCT, randomized clinical trial; WHO, World Health Organization