

Appendix 4: Examples of methodological problems that could not be corrected.

Study Id	Intervention	Contol	Assessed outcome	Blinding of patients/ care providers	Methodological issue related to blinding of patients/ care providers
Bujko 2006	Preoperative irradiation for rectal cancer	Radiochemotherapy, with two courses of 5-fluorouracil and leucovorin prior surgery	Local recurrence	No blinding	No blinding, treatments with very frequent and clinically specific side effects: when some people receive chemotherapeutic agents and some do not we considered that this can be a potential source of bias, and due to the very specific and frequent side effect of chemotherapy this problem was thus impossible to solve with a methodological adjustment
Gerard 2006	Preoperative radiotherapy in resectable T3-4, Nx, M0 rectal adenocarcinoma	Preoperative radiotherapy , and chemotherapy with fluorouracil and leucovorin, in resectable T3-4, Nx, M0 rectal adenocarcinoma	Local recurrence	No blinding	No blinding, treatments with very frequent and clinically specific side effects: when some people receive chemotherapeutic agents and some do not we considered that this can be a potential source of bias, and due to the very specific and frequent side effect of chemotherapy this problem was thus impossible to solve with a methodological adjustment
Blackburn 1981	Interruption of tranquilizing medication among schizophrenics patients	Patients usual treatment was replaced by placebo tablets, as placebo was physically different from the regular treatment, patients were told they were under a new drug.	Relapse, at anytime	Placebo was used (named CAT)	Double, thiamine chloride was used as placebo, participants and nurses were told that a new medication was given, but "It was noted, however, that nursing personnel were soon referring to CAT as a placebo"
Morton 1968	Chlorpromazine or trifluoperazine withdrawal in chronic schizophrenia	Patients' usual treatment was replaced by placebo tablets. Placebo was identical tablets, with no taper period	Relapse, at anytime	Placebo was used. Identical tablets, prepared by the hospital pharmacist, were used	Trial authors reported that nurses made correct guesses as to who was on drug and who was on placebo.