Relapse prevention (long-term) studies: what happens after drop out?

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Disclosures

In the past 3 years:

Consulting/advisory board honoraria from LB Pharma, Lundbeck, Otsuka, Roche, and TEVA
Lecture honoraria from AOP Orphan, ICON, Janssen, Lilly, Lundbeck, Otsuka, Sanofi, Roche, and Servier
Publication from Roche

Relapse prevention (long-term) studies: what happens after drop out?

We don't even know whether patients drop out if they relapsed

Leucht et al. Relapse prevention with antipsychotic drugs compared to placebo, Lancet 2012

The problem

- **Drop-out rates in randomised mental health trials are high**
- **For example, the average dropout rate in a meta-analysis on antipsychotic drug trials for acute schizophrenia (212 RCTs, 43000 participants) was 35% (Leucht et al. Lancet 2013).**
- **The dropout rate of a meta-analysis comparing antipsychotic drugs with placebo for relapse prevention at 9-12 months was 41% (Leucht et al. Lancet 2012)**

The problem

- **It is questionable whether even the best statistical models (MMRM, multiple imputation, survival analysis etc) can fully account for so high dropout rates**

- **Some, e.g. Cochrane Schizophrenia Group, does not accept studies with so high dropout rates in its systematic review, saying that the are „not credible“**

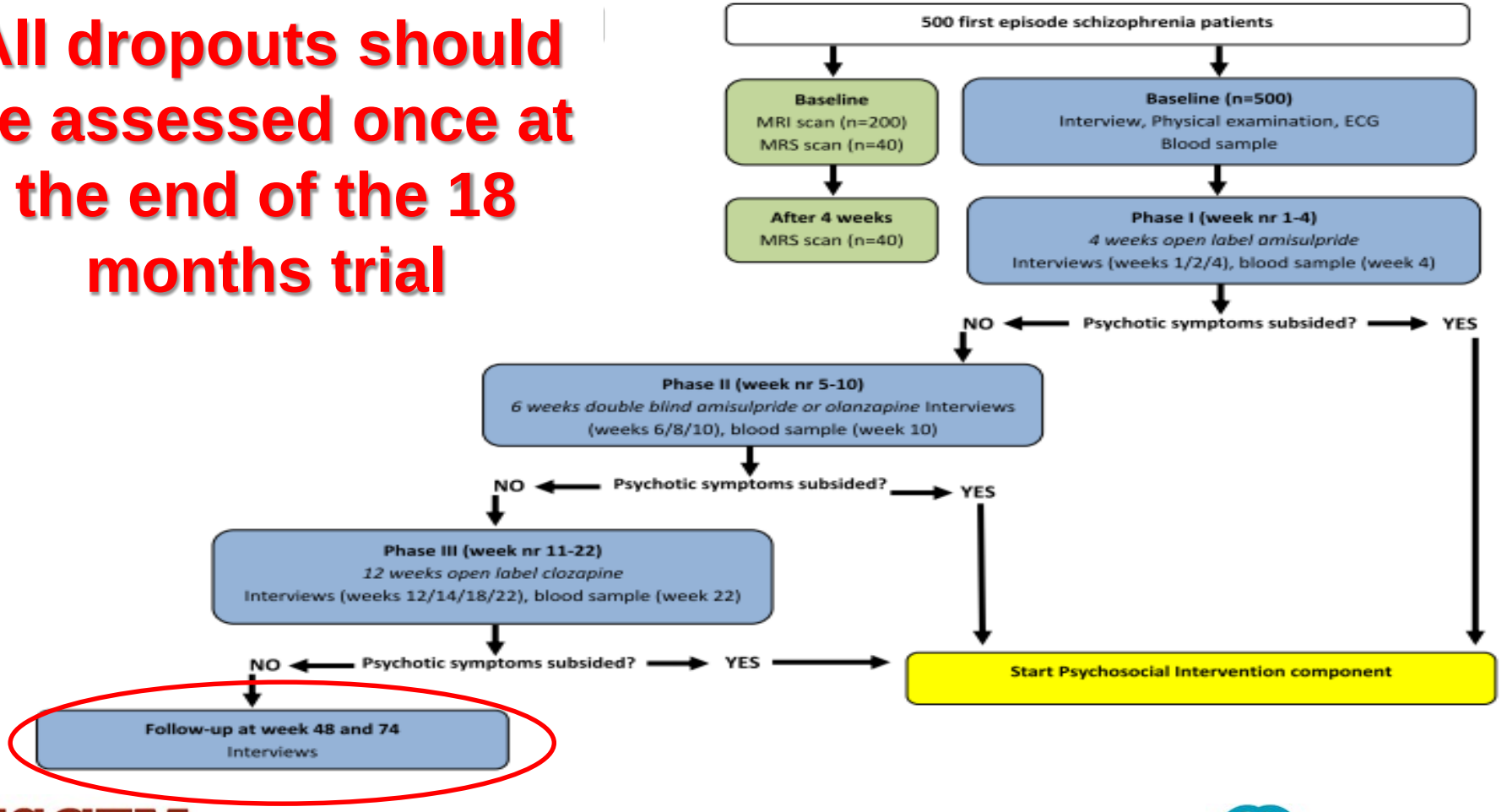
To know what happened to the dropouts would be very interesting for several reasons, for example:

- **Such a procedure would be closer to the intention-to-treat principle, meaning that all patients who have been randomised should followed up**
- **If dropouts are then treated in routine care, is their outcome worse or better than that who stayed in the protocol?**
- **Little has been done in this regard so far**

OPTIMISE study

(EU funded, 500 first episode patients with schizophrenia, PI R. Kahn)

All dropouts should be assessed once at the end of the 18 months trial



Only very few dropouts could be followed at 18 months with this „lose“ design

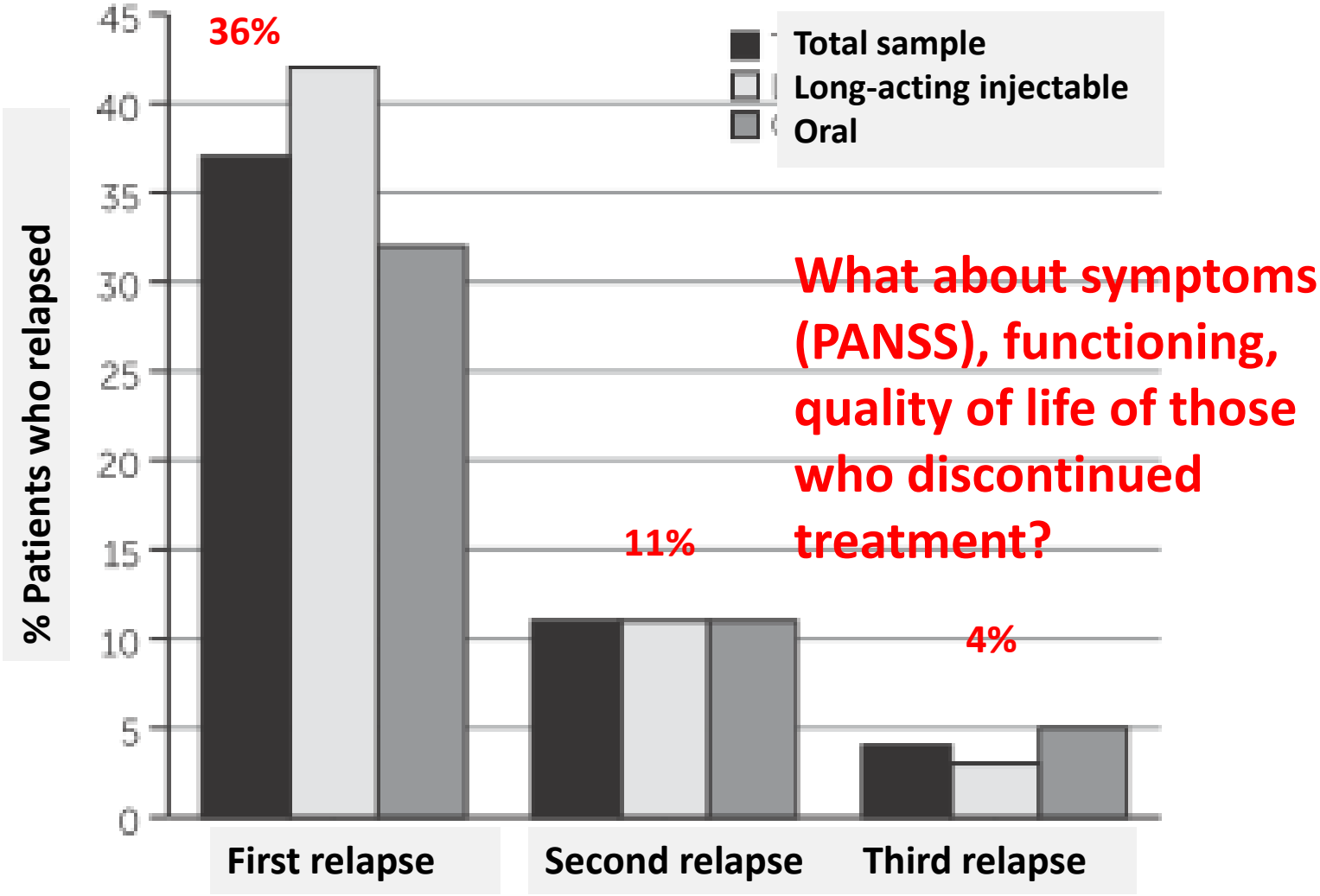
It seems that once patients have left the study path, it is difficult to reach out to them

PROACTIVE study (risperidone Consta vs oral antipsychotics for relapse prevention,

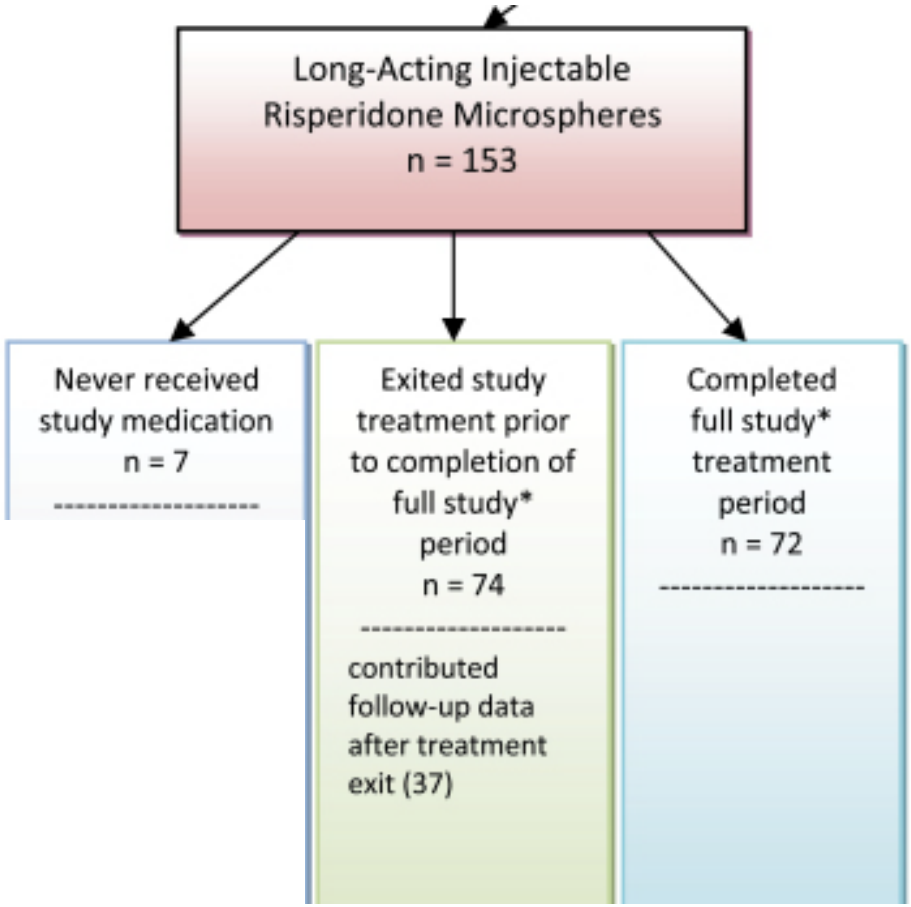
305 patients, 30 months, Buckley et al. Schizophr Bull 2016)

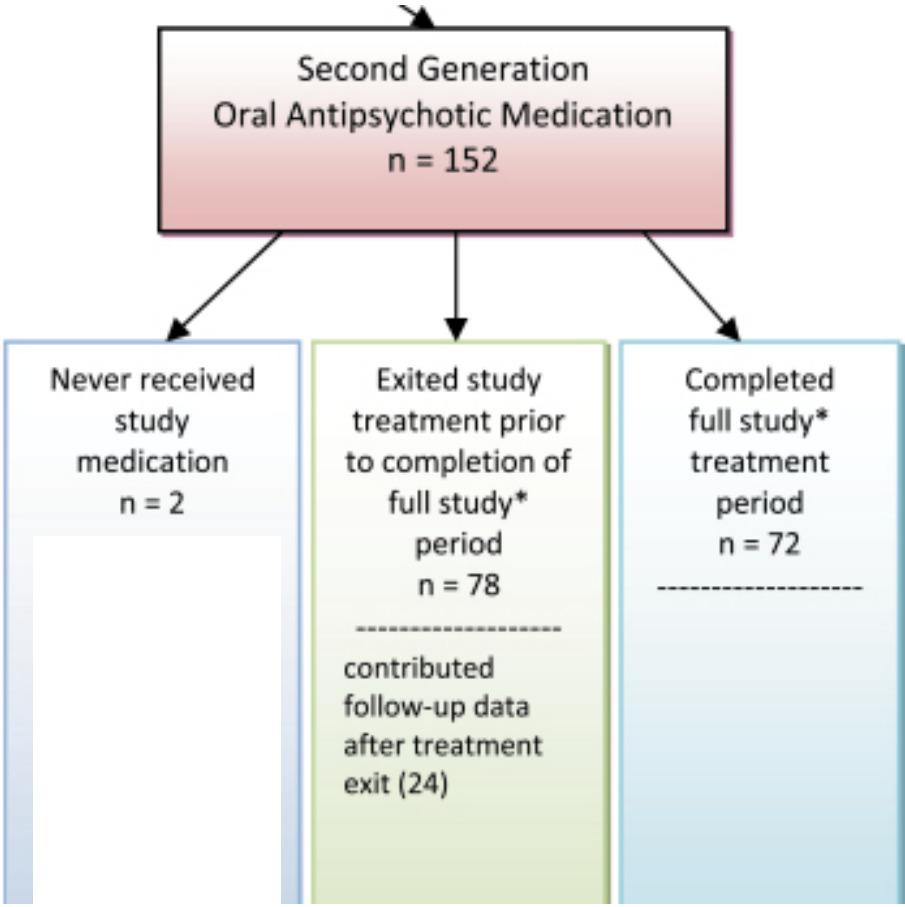
- All patients discontinued treatment should be followed with the same procedures
- Relapse did also not require discontinuation of the study

Subsequent relapses among patients who had relapsed and who continued in treatment follow-up, or both



What about symptoms (PANSS), functioning, quality of life of those who discontinued treatment?





Of 152 (50% of randomised sample) patients who exited study treatment before study completion only 61 (40%) contributed follow-up data after treatment exit

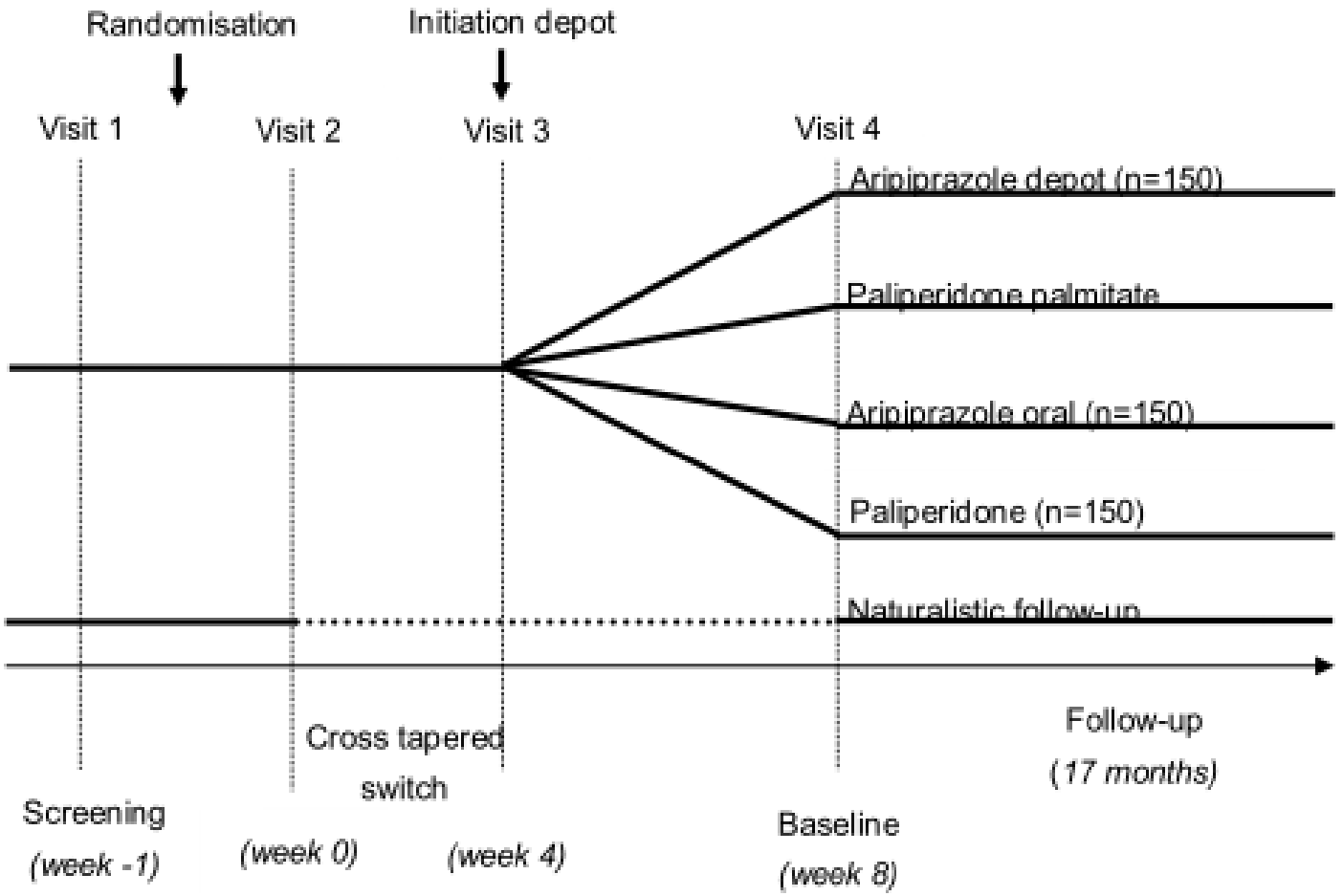
Why did only 60 (40%) of the relapsers stay in the study, although the protocol was designed to keep them in?

Relatively broad reasons for study discontinuation?

- Serious adverse events
- Life-threatening adverse event (AE)
- Serious and/or life-threatening clinical circumstances (e.g., uncontrollable violence or suicidal behavior and/or severe relapse)
- Withdrawal of consent
- Loss to follow-up
- Serious protocol violation
- Administrative reasons

EULAST – Study

Aripiprazole LAI vs paliperidone LAI vs their oral formulations
600 patients with early schizophrenia, 18 months follow-up
primary outcome all cause discontinuation



EULAST – Study

I. Design component

- **Patients meeting discontinuation criteria stay in the study with the same visits**
- **Withdrawal from the study only occurs in specific cases (e.g. withdrawal of consent, pregnancy, changed to involuntary treatment)**

II. Design component

- **Patients who do not consent can enter an additional protocol with a completely**
- **naturalistic follow-up**
- **With the idea to compare the study population with the routine care population**

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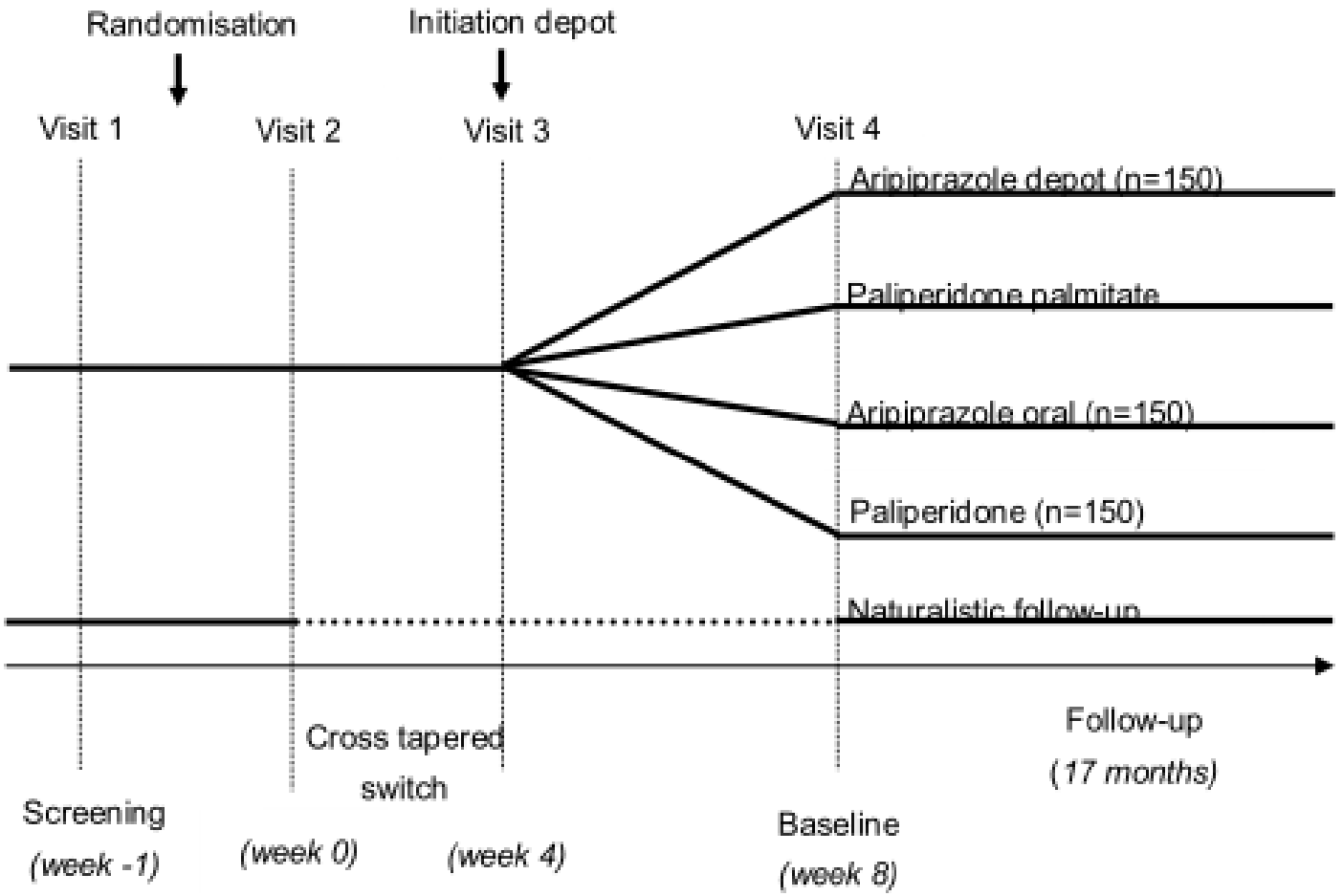

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Conclusions

- **More studies should follow-up patients who relapsed or who discontinued the original protocol**

- **A few studies have addressed this issue, but there is a lot of uncertainty as to this should be done**

I. Allowing patients to cross-over to the other arm

- Frequently used in cost effectiveness studies
- Patients are allowed to cross over to the other arm and are still analysed as being in the original arm in the ITT analysis
- Aim: to keep as many patients as possible in the study
- Problem: it is not really possible to find out whether a drug is effective (or ineffective)
- The design only measures whether the initial randomisation to a drug leads to a better outcome
- It may work in other areas, e.g. cancer, but in psychiatry it is difficult
- Solution: sensitivity analysis of the stayers only. But this is often made only for the primary outcome

Cross-over example: Rosenheck et al. JAMA 2003

- 309 patients with schizophrenia randomised to either olanzapine or haloperidol + benztropine for 12 months
- ~60% discontinued the assigned treatment
- ~25% of these discontinuers could be followed up for the entire 12 months
- No significant difference in overall retention rate (primary outcome) or symptoms