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Comment

Intention-to-treat has implications for study planning and execution, not just subject retention and follow-up

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Van der Weijden et al. (2008) make three arguments against intention-to-treat (ITT): in a trial intended for ''proof of principle'', ITT may obscure the relevant test; ITT may give investigators an incentive to coerce subjects; and because adherence in a study may differ from adherence in practice, ITT may give a misleading result. This comment addresses each of these arguments.

To begin, the notion of ''proof of principle'' seems vague to a fault. Here are two examples in which ITT was violated for the sake of proving a principle, in both cases giving the wrong result in terms of patient outcomes.

Lopez et al. (2002): In this study, pregnant women with periodontal disease were randomized between immediate and post-partum periodontal therapy (treated and control groups, respectively). The primary analysis – incorrectly described as an ITT analysis (Table 4, Lopez et al. 2002) – included only women who had live births, excluding randomized subjects who had spontaneous abortions or miscarriages. In this analysis, 2 of 163 pregnancies in the treated group (1.1%) were pre-term, while 12 of 188 pregnancies in the control group (6.4%) were pre-term ($p = 0.017$), proving the principle that periodontal therapy reduces live pre-term births. But if we include women who had non-live births – 13 and 8 in the treated and control groups, respectively – and perform a true ITT analysis of the fraction having an undesirable end to the pregnancy, the result changes: 15 of 176 of treated women (8.5%) had bad outcomes, 20 of 196 control women (10.2%) had bad outcomes, and $p = 0.60$. In proving their principle, the authors got the wrong answer: periodontal therapy did not improve pregnancy outcomes.

Chaisson et al. (1994): This phase I study tested clarithromycin for treating *Mycobacterium avium* complex (MAC), a late-stage AIDS-defining disease. At the time, patients with MAC lived a median of about 6 months after diagnosis. This study considered three doses of clarithromycin, 500, 1000, and 2000 mg, each twice daily, with primary outcome clearance of *M. avium* from blood, ascertained by blood draws every 2 weeks. This outcome necessarily implies a non-ITT analysis because dead persons do not give blood draws. In the 2000 mg arm, so many patients died that this dose was declared unsafe. Among those alive for follow-up blood draws, a lower fraction receiving 1000 mg had detectable *M. avium* compared with 500 mg, proving the principle that the higher dose killed bacteria more effectively. This was the main basis for the US FDA's approval of clarithromycin for treating MAC, though this was controversial (Goldberger & Masur 1994) largely because patients tended to die earlier on 1000 mg than on 500 mg ($p < 0.05$ for a Wilcoxon test but not a log-rank test). A later study (Cohn et al. 1999) confirmed higher hazard of death on 1000 mg bid than on 500 mg bid – the higher dose produced worse patient outcomes despite more effective anti-bacterial activity – and standard-of-care became 500 mg bid.

What do these examples imply about ITT? To argue that violating ITT is needed to prove a principle, we must accept the principle's legitimacy; in these examples, that would imply taking each study's design as given. But of course, these designs were chosen, not given. By construing ITT in this narrow way, as merely relevant to a study's analysis, we ignore the most important aspects of a study. To their credit, the authors take a broader-than-usual view of ITT, by suggesting it gives investigators an incentive to coerce patients. But this is still too narrow: rather, investigators should have ITT in mind from the first moment of study planning. Doing so might reduce or even eliminate the apparent contradiction between ITT and subject autonomy. The rest of my comment elaborates this point while addressing the authors' argument about adherence to therapy in practice.

How is study planning affected by prospectively considering ITT?

(1) Choice of outcome: As the examples indicate, the principle ''a new treatment should improve a patient's welfare'' affects the choice of outcome measure. Generally speaking, an outcome that broadly captures a patient's welfare lends itself more readily to ITT. The

examples suggest ITT is an inconvenience when we would like to ignore certain aspects of patient welfare.

(2) Patient care during the study: If ''adherence during a trial might be quite different from adherence once a treatment has been proven effective'', this suggests the trial was designed poorly. Poor design can create incentives for non-adherence, or can specify concomitant care so narrowly that patients are forced out of the study needlessly. Instead, studies should be as close as possible to clinical practice and should not, as is all too typical, attempt to control treatment to the point that conditions are unrealistic and increase or even create non-compliance. (Besides, recent developments in statistical methods allow adjustment for the effects of adherence while maintaining the ITT principle. See, for example, Jin & Rubin 2008.)

(3) Incentives for investigators: Allowing deviation from ITT because of non-adherence creates a bias in favor of finding a treatment effect, which is said to increase a publication's chance of acceptance and presumably does not displease corporate sponsors. By disallowing post-hoc excuses for poor follow-up, ITT gives investigators an incentive to design and invest in effective follow-up. The authors' alternative to ITT removes this incentive by letting investigators present the analysis they find most favorable and hope the journal and the relevant audience are willing to overlook deficiencies in follow-up.

(4) Incentives for subjects: A study's design creates incentive for subjects. In a wisely-designed study, subjects will see an advantage to themselves in behavior that improves the study's validity, in particular staying in the study. For example, subjects should receive some benefit as long as the investigators follow them, even after they drop off study treatment. In the United States, free health care is an important way to do this; in countries with universal health care, paying subjects is appropriate and effective. Wise design also makes it easy for subjects to participate, for example by having study events occur at their primary care centers and not at a referral center that is more convenient for the investigators. Further examples are easy to find, if investigators can be bothered to look. Finally, a study's design should never give subjects an incentive to lie or to withdraw, as happens, for example, when benefits are withheld if subjects deviate from protocol even in a small way.

Therefore, while I do not assert that a proof-of-principle argument for violating ITT is never compelling, I would argue that the burden of proof is on those claiming a need to violate ITT, that the burden should be extremely high, and that any planned per-protocol analysis should be registered before randomization begins. Given the human capacity for rationalization, such a proof-of-principle argument should never be considered after the first patient is randomized.

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