Reviewer’s report

Title: Evaluation of real-world evidence for the effectiveness of academic detailing on appropriate prescribing of pain relief medication in Belgian general practices: a cluster randomized trial

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Reviewer: Sabine Landau

Reviewer's report:

This is a cluster randomised trial to evaluate the effectiveness of an academic detailing visit by Farmaka ADS on prescribing of pain relief medication. This is a reasonably well-written paper, although the presentation might be improved by a clearer structure (lists, headings etc.) instead of long text paragraphs.

The intervention was allocated at the GP practice level (cluster). Summary patient outcomes were also determined at the GP level.

My main criticism regarding the reporting of this cluster randomised trial is that the primary outcome (or outcomes) have not been defined. Instead a time series of monthly pre- and post-intervention measures is modelled using a fairly complex approach and various parameters are tested, but without clarification as to why these parameters would provide evidence of effectiveness.

Detailed comments:

Trial design:

3529 practices were randomised but only 1698+1703 practices were included in the analyses. I assume this is because "GPs were given the option to opt out from the analyses". This seems an unfortunate design choice/consent procedure. All the problems associated with non-random treatment allocation are potentially re-introduced by creating non-response informed by treatment allocation. Why were GPs who were not willing to take part in the study not excluded before randomisation to safeguard the internal validity of the trial?

Why were the practices sorted by age of GP before randomisation? Are the blocks of two to represent age strata? You mention creating "a comparable spread of visit dates" but the control group does not receive any visits?
Methods:

The presentation might benefit from a list of measures (bullets, table etc.)

Analysis approach/Figure 2:

This section would benefit from a clearer description of the research questions asked and the approaches used to address them. The analyses labelled ITT1 and ITT2 are not intention to treat analyses as not all observed subjects are analysed in the groups to which they were randomised. I would consider all of ITT1, IIT2 and PPR per-protocol approaches based on different definitions as to what constitutes a protocol violation. I would assume that the analyses are carried out for different purposes? If their purpose is to also evaluate efficacy (=the effect of receiving a detailing visit) the there might be better ways of achieving that.

Statistical methods:

It is not clear whether repeated measures/multilevel modelling or time-series methods are used here and how they are motivated. Time-varying explanatory variables cannot be the motivation as trials do not typically require adjustment for baseline variables. There is some mention of using a "working correlation matrix" which hints at the use of GEE (presumably with robust standard errors)?

The analysis seems overly complex and does not target a clearly defined primary outcome. Which of the 6 model parameters represent measures of effectiveness and are therefore are of interest here? I would expect the objective of a clinical trial analysis to be demonstrating that an intervention has an effect on a primary outcome measured at a specified post-randomisation time point.

There are a number of subgroup analyses. I am not sure that these are necessary. In addition, any modification assessment would need to be modelled by various interaction terms.

How does the analysis deal with missing data? What assumptions are made?

A number of baseline variables were used in the randomisation procedure. Was this acknowledged in the analysis approach?

Results:

This section implies that the estimates of interest are step change = difference before and after the intervention and change in trend = monthly change after the intervention (see table 2). I
would be looking for comparisons between trial arms. I was not able to understand the meaning of the effects quoted in table 2.

The results section discusses change over time, which would not be relevant in the context of establishing effectiveness.

If the effects quoted in tables 2 and 3 for proportion outcomes represent odds ratios then I would be concerned about their clinical relevance. Two significant effects seem to indicate a reduction of 2%?

Even though the primary outcomes have not been clearly specified, there are at least four (more if several months are of interest). No adjustment for such multiple comparisons has been applied.

Tables 4 and 5 labelled "covariate effects..." are simply provided and not referred to in any detail. I was unable to understand their purpose.

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