Author’s response to reviews

Title: European youth care sites serve different populations of adolescents with cannabis use disorder. Baseline and referral data from the INCANT trial

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Response to reviewers’ reports

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Europe is heterogeneous. The influence of transnational care policy differences on baseline characteristics of adolescents with cannabis disorder in the INCANT trial. Olivier Phan, Craig E Henderson, Tatiana Angelidis, Patricia Weil, Manja van der Toorn, Renske Rigter, Cecilia Soria and Henk Rigter

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GENERAL COMMENT BY THE AUTHORS

We plan to publish INCANT papers on (a) the design of the study (has already been published by BMC Psychiatry 2010, 10:28doi:10.1186/1471-244X-10-28); (b) baseline characteristics of study participants (present manuscript); (c) content analysis of TAU (treatment as usual) as delivered in the five INCANT sites/countries; (d) treatment retention; (e) primary outcome data; (f) secondary outcome data; and (g) implementation of MDFT in Europe.

Some of the questions by the reviewers pertain to study design and to study outcomes other than baseline measurements. We have revised the manuscript to include some of the information in which the reviewers showed interest, without shifting the focus of the present paper. Other information is given below.

REFEREE 1 (W Vollebergh)

Comment # 1: “The description of the characteristics (..) is very basic. Only percentages are given.”
Response # 1: Our choice to present percentages in the tables and text was for readability’s sake. If we had also added N per cell (number of study participants), this would have been confusing because sites differed in total N (from 60 in Belgium and Switzerland to 120 in Germany). For instance, a number such as 60 would have meant 100% in Belgium and 50% in Germany.

In the revised manuscript, we still use percentages. If wished, we will upload the detailed tables (including Ns) as additional files at the end of the manuscript, a possibility we discussed with the Journal Editorial Office.

Comment # 2: “Add more advanced statistics.”

Response # 2: We agree with the reviewer’s request for more advanced statistics.

We have performed Multivariate Analysis of Variance (MANOVA) targeting a combination of baseline variables from measures (TLFB, YSR, CBCL) that will also feature in the outcome analyses of INCANT. MANOVAs are appropriate for dependent measures that are presumed to be at least moderately correlated with each other.

The TLFB, YSR and CBCL yield continuous data, which can easily be combined in a multivariate model. In contrast, categorical data, such as the data for which we report chi-square tests, are notoriously messy and difficult to interpret in multivariate models. Moreover, multivariate models consisting of categorical data cannot address the central methodological question of the current study; that is, can we account for cross-site heterogeneity in a way that makes reporting cross-site outcome analyses possible?

Comment # 3: “Do the authors think their effort to compare across countries was impacted by the difference in referral?”

Response # 3: Referral type had an impact; this is the message of the manuscript. Presumably, the referee wonders if the impact of referral policy was such, that no decent across-countries comparison could be made.

This is an important question that goes beyond INCANT: is any cross-national youth care trial possible in Europe considering the variations in referral policies? Our manuscript shows that it is possible to statistically correct for referral policy differences without affecting the across-site comparability of treatment results. Cross-national European trials appear to be possible. In our revision of the manuscript, we have given this issue more emphasis in the Discussion section.

Considering the INCANT outcome data (which will be described in other papers), we know that MDFT and Treatment As Usual (TAU) were effective at all sites, and that MDFT was superior to TAU across sites in adolescents with high-severity problem behaviour on key outcome measures. Referral policy was important in interpreting outcomes, but was no major factor in determining treatment effectiveness.
Important to making treatment comparisons across sites, there were no significant treatment by site interaction effects in our outcome analyses—indicating that the relative treatment differences across time were similar across sites.

Comment # 4: “Although this is not the focus of the article, I keep wondering how the effect of a treatment can be compared across countries when TAU is as different as described”

Response # 4: This indeed is not part of the present manuscript.

We are puzzled by this comment, as the present manuscript does not describe TAU (and correctly so, because the baseline assessment was pre-treatment). Perhaps, the referee was referring to information in other documents.

Though not part of the present manuscript, we are pleased to say something about TAU in this cover letter.

It is not uncommon in across-site treatment trials to allow each site to practice its own TAU (otherwise, TAU wouldn’t be TAU).

TAU differed between INCANT sites (CBT and psychodynamic), but we made sure that all forms of TAU had in common that they strongly differed from MDFT in not being a systems therapy, e.g., not offering sessions with the parents or the family (just sessions with the adolescent alone). This intended contrast was achieved, as the planned papers on TAU and on treatment retention will show.

Still, TAU in the Netherlands (cognitive behavioural therapy; CBT) was not the same as TAU in France (psychodynamic), for instance. We know from the INCANT outcome data that TAU-CBT was as effective as TAU-psychodynamic, and that MDFT was superior to TAU on various measures irrespective of the theoretical orientation of TAU. Therefore, the referee’s worry is not vindicated by the INCANT findings.

Comment # 5: “Are the authors not trying to present their data as being part of 1 large RCT, (..) [while really] describing the effects of 5 RCT’s that only have the experimental treatment in common”

Response # 5: This also bears on another comment by this referee (statistical power), which we address here as well.

No, INCANT was not planned as a collection of 5 different trials. Power calculations have been described in our BMC Psychiatry design paper (see above). In our computations, each site needed to recruit 100 cases for an effect size difference between MDFT and TAU of $d = 0.7$ and power level of 0.82 (120 cases for power level 0.88).

The Belgian and Swiss governments did not have the money to have 120 cases recruited in their countries. They settled for $N = 60$ each, explicitly signing in on across-site statistical analyses.
In the INCANT study protocol (www.incant.eu), the joint trial thought has been leading and is still leading in the outcome analyses. Of note, all study procedures (informed consent, measurement instruments, assessments, etc.) were identical between sites to render across-site analyses possible.

The INCANT sites had more in common than just the experimental treatment. See also Comment # 4 above.

In the revision, we have included information on power calculations in the Methods section (bottom of p. 6, top p. 7), where also the 1-trial ambition has been described.

Comment # 6: Smaller issue. “I would like to see more information about MDFT”

Response # 6: We have added information on MDFT (Background section, middle of p. 4; revised manuscript).

In this manuscript, we are not discussing the position of MDFT amidst other treatment programmes (we will do so in our implementation paper).

PMT (mentioned by the referee) does not resemble MDFT and is not part of the same research literature.

Like MDFT, MST is a systems therapy for adolescents with problem behaviour. The five European countries that were planning to select a therapy for examination in Europe, had a thorough literature analysis done and convened a meeting of international experts. MST was considered, but the evidence was judged to favour MDFT (Spruit IP [Ed]: Cannabis 2002 Report. Brussels: Ministry of Public Health of Belgium; 2002).

Comment # 7: “Smaller issue. There is no abbreviated YSR.”

Response # 7: The word ‘abbreviated’ is misleading and we have deleted this term in the revision. What we meant is that we did not use all scales of the YSR.

We have been using the ‘internalizing’ Anxiety/Affective and the ‘externalizing’ Aggression/Delinquency scales of the YSR, as they tap specific risk factors for problem behaviour in the adolescents targeted by INCANT. The full YSR as a whole has been found valid and reliable, but the scales selected for INCANT are also valid and reliable as shown in various languages and countries. We have revised the text (top of p. 9) and have added references to relevant literature.

Comment # 8: “Smaller issue. Not all adolescents had cannabis disorder (84% in the Netherlands, for example)”

Response # 8: This is a misunderstanding. 84% had the diagnosis cannabis dependence; 16% had the other cannabis use disorder diagnosis: cannabis abuse. This has been clarified in the revised text.

Comment # 9: “Smaller issue. Several hurdles are mentioned on p.4. How were they overcome?”
Response # 9: The hurdles are already mentioned in the paragraph concerned. The reviewer asks how the hurdles were overcome. This is not the topic of the present manuscript, but it will feature in our implementation paper. Diplomacy and a good feeling for the interface between research and policy have been essential in making INCANT work.

Comment # 10: Smaller issue: more information on recruitment, please.

Response # 10: In the manuscript, we have reported recruitment stringently adhering to the instructions/suggestions of CONSORT (Consolidated Standards of Reporting Trials group; www.consort-statement.org). In the revised text, we have added more descriptive detail.

The reviewer asks about the “response rate”. We assume this meant: the proportion of adolescents who at baseline were assessed to have a cannabis use disorder agreeing to participate (like their parents) in the study. We have added this figure (75%) to the text. The manuscript already listed the reasons for not accepting the offer to take part in INCANT: no informed consent, moving out of sight, etc.; this text has not been changed.

REFEREE 2 (D Hedrich)

This referee rightly corrects us for a tendency to equate ‘site’ with ‘country’.

We have not addressed this critique by arguing (for instance) that the adolescents we recruited in Geneva were representative for all of Switzerland, or that a particular referral process in Berlin was typical for all of Germany, or that cannabis treatment need at a specific site reflected all cannabis treatment need in that country. A RCT has internal validity, but it can never pretend to have the external validity that is needed to ensure that the trial’s outcomes would be relevant for a whole country.

We adopted the comments of the referee by strictly limiting the text and the arguments to ‘sites’ rather than ‘countries’.

Accordingly, we did change the title of the manuscript, which now reads:

“European youth care sites serve different populations of adolescents with cannabis use disorder. Baseline and referral data from the INCANT trial”

Comment # 1: Explain the process reclassifying referral type in more detail.

Response # 1: In the revised manuscript, we have given this suggestion full credit. The information requested has been added to the Methods section on p. 9 and 10.

The term ‘professional’ (as one of the referral sources) was apparently confusing. A professional can be a social worker, for instance. In some countries, a social worker can be a therapist, or a youth probation officer, or someone at a Youth Care intake/referral agency. The discipline of the professional is not crucial here,
but his or her position within a particular agency is. We have decided to drop the term ‘professional’. So, in Table 4 of the revised manuscript the column ‘Professionals’ has now been renamed ‘Treatment and care agencies’ (short for: referral by a professional working at another treatment or care agency).

Comment #2: Make more clear in the Discussion how specific the recruitment process was (e.g., that Paris does not stand for all of France; that a high rate of Justice-referrals in Geneva does not stand for referral in all of Switzerland).

Response #2: We have revised the Discussion according to this recommendation (see new paragraph: Sites are not the same as countries). The emphasis of the manuscript is now on sites, rather than on countries, and we avoid any suggestion that site differences coincide with differences between countries.

On behalf of the authors,

H Rigter