Author's response to reviews

Title: Protocol for a randomized controlled trial to study the efficacy of a brief intervention to reduce alcohol misuse in patients with HIV in South Africa.

Authors:

Diana Huis in 't Veld (dhuisintveld@itg.be)
Linda Skaal (Linda_Skaal@embanet.com)
Karl Peltzer (kpeltzer@hsrc.ac.za)
Robert Colebunders (bcoleb@itg.be)
John V Ndimande (ndimande@gpnet.net)
Supa Pengpid (Supa_Pengpid@embanet.com)

Version: 4 Date: 7 September 2012

Author's response to reviews: see over
Pretoria, 05-09-2012

Regarding: manuscript entitled: Protocol for a randomized controlled trial to study the efficacy of a brief intervention to reduce alcohol misuse in patients with HIV in South Africa.

Dear Reviewer, dear Editors,

Thank you very much for the valuable review of our manuscript. We addressed the comments below and made changes in the manuscript. We hope this improved the manuscript, but additional comments are welcomed.

Reviewer's report

Title: Protocol for a randomized controlled trial to study the efficacy of a brief intervention to reduce alcohol misuse in patients with HIV in South Africa.

Version: 1 Date: 9 August 2012

Reviewer: John Norrie

Reviewer's report:

Protocol for a randomised controlled trial to study the efficacy of a brief intervention to reduce alcohol misuse in patients with HIV in South Africa

Discretionary revisions

1. The reported numbers for the per capita consumption of alcohol at 40 litres of pure alcohol for men and 24 for women are astonishing – to the point that you wonder if they are correct – several points:

   Author response: Indeed, the numbers are extremely high, but this information is based on what is reported in the WHO/United Nation report on substance use for South Africa.

   a. This is the average amongst those that drink – so what is the overall average per head of adult population (or, what is the estimated proportion of men and women that do not drink).

   Author response: The adults (15+) per capita consumption, average 2003-2005 in South Africa is 9.5 litres of pure alcohol (for the whole WHO Africa region it is 6.2 litres of pure alcohol). This information is added in the “Background” text of the manuscript.
Here the table for the percentage of abstainers in South Africa (reference 2)

<table>
<thead>
<tr>
<th>ABSTAINERS (15+ years), 2004</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime abstainers</td>
<td>51.0%</td>
<td>78.6%</td>
<td>65.2%</td>
</tr>
<tr>
<td>Former drinkers</td>
<td>9.5%</td>
<td>6.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Abstainers*</td>
<td>60.5%</td>
<td>84.6%</td>
<td>72.9%</td>
</tr>
</tbody>
</table>

* Persons who did not drink in the past 12 months.

b. Even allowing for this, 40 litres of pure alcohol is around 100 litres of whisky – that is around 4 standard bottles of whisky a week – and this is the average, which even allowing for a heavy skew, still will mean that there must be many men drinking more than that?

**Author response:** If assuming that a bottle of whisky contains 40% alcohol, it would indeed be 100 litres of whisky per year, which is about **2.5 bottles** (750 ml) of whisky per week, which indeed is a very high consumption.

Consumption in heavy episodic drinkers (at least 60 grams or more of pure alcohol on at least one occasion weekly) (15-85+year), **males**, 2003: 48.1%

Consumption in heavy episodic drinkers (at least 60 grams or more of pure alcohol on at least one occasion weekly) (15-85+year), **females**, 2003: 41.2%

(see reference 2)

c. Is alcohol in South Africa very cheap, because these levels of drinking wouldn't even seem affordable, particularly in a LMIC context, let alone incapacitating and hugely harmful to health?

**Author response:** I am not aware of the average prices of liquor, but to give an indication of minimum prices (cheap brands):

- beer: can 340 mL: from ZAR 5.00 (about USD 0.60)
- wine, bottle 750 mL: from ZAR 15 (about USD 1.80)
- whiskey, bottle 750 mL: from ZAR 70 (about USD 8.60)
- many people in township brew their local spirits, with relatively cheap ingredients

These prices seem relatively low, but with a high unemployment rate in South Africa and low average incomes in people with lower economic status, the total expenditure on alcohol in users might comprise a substantial part of the household budget. We agree, this might have significant negative health effects.
d. The reference given [2] seems to be a WHO datasheet about HIV/AIDS – is this the right reference?

Author response: The reference is indeed not the right one. It is corrected to the right reference; a WHO datasheet on substance abuse.

2. It would be useful to have a paragraph or two on how generalisable the findings are likely to be – how these 500 or so recruits from the primary care clinics in townships in Guateng are likely to be representative of the identified subset of ‘problem drinkers’ with HIV-1 (a) across the rest of South Africa and then (b) across Africa and then (c) globally for all those with HIV-1 who have drink problems?

Author response: An additional part on generalizability of the results is added to the manuscript in the “outcomes”-section, stating: “The findings will be important in the public health setting. The AUDIT screening tool is developed by WHO and proved to be applicable in a wide range of settings and target groups, including HIV patients in South Africa. The brief intervention we propose was also developed by WHO and was proven to be successful in different settings [41]. This makes the intervention widely applicable in different settings and regions. However, the intervention was never tested among patients with HIV infection in South Africa, which this trial aims to do. If the intervention proofs to be efficient, it could potentially be incorporated in the South African HIV care guidelines. The generalizability of the trial result may however not be extended to other countries, where there might be different patterns of alcohol consumption and different cultural beliefs regarding alcohol use and medical care.

3. One specific issue about possible selection bias is that the study can only access participants who are attending the clinics – what about HIV-1+ patients who are getting treated but their drinking is contributing to unreliable and sporadic attendance at the clinics, or even more extreme their drinking has meant that they have stopped attending the HIV-1+ treatment clinics? Although their drinking levels may have excluded them from the study anyway, nonetheless there would seem that there may be a possible group of relevance there that could be missed?

Author response: Indeed there is a selection bias. This intervention will not reach patients who (maybe related to issues regarding their alcohol abuse) do not attend the clinics. If the intervention proofs to be successful, it could be carried out in patients that do attend clinics (even sporadically), with a possible positive effect in the patients that use hazardous levels of alcohol (according to AUDIT scoring). The patients with harmful levels of alcohol consumption are excluded from this study, so the results will not be applicable to this group.

4. Page 6 – the aims of the study are a bit confusing to read until you realise that the study is first a screening study which will capture data on everyone with HIV-1 at the clinics (so for example the study can estimate the prevalence of drinking behaviours), and then having identified the problem drinkers within a certain range on AUDIT, who aren’t in alcohol treatment or have any of the comorbidities listed for exclusion, proceed to randomise just this subset. It would be useful to make this
‘screening -> then randomised trial’ design more explicitly clear.

**Author response:** the study design is explained in more detail (page 6). It is divided in two sections: a ‘screening phase’ and an ‘intervention phase’, to make the study design more clear. Also the “Objectives” part is divided in these two phases: ‘screening phase’ and ‘intervention’ phase

5. Page 6 ‘... between pre-intervention, 3 months and 12 months after intervention’ – over what period is the pre-intervention defined?

**Author response:** in the part that describes the “Design” of the study, the term ‘pre-intervention’ is introduced and explained: “…where information from patients will be collected at inclusion (before the intervention which is performed in the same session: pre-intervention) and at follow up at 3 and 12-months.”

6. The authors introduce the phrases ‘harmful’ and ‘hazardous’ drinking, which seem to have agreed and quantifiably distinct definitions – but by the Discussion are using the term ‘problem drinker’ – useful to define terms and then be consistent throughout?

**Author response:** Hazardous- and harmful drinking are the terms that are used in the AUDIT questionnaire, which we use in our study. In the “Background” section, we use the terms describing alcohol use or the severity of alcohol use which are used in the original articles, because screening methods differ in different studies. However, in the “Methods” section we changed the more general terms for alcohol use and severity of alcohol use to the terms “hazardous- and harmful alcohol use”.

7. The sample size calculation needs to be explained more carefully – the randomised trial is in a carefully defined subset of problem drinkers, and yet the authors seem to justify the power calculation’s assumed effect size in terms of comparing drinkers with non-drinkers. They need to explicitly discuss what proportion of that difference it would be reasonable to expect a brief intervention would realise, and then justify that reasoning?

**Author response:** We recalculated the sample size. The text is adapted in the manuscript under the heading “Sample size calculation” (page 8): “Based on the current AUDIT score of 12 among HIV patients, it is assumed that the intervention will reduce the current AUDIT score by 12% to 10.6 [32, 33]. Based on this assumption the estimated sample size of N will allow us with 80% power (5% level of significance) to detect the difference of 12% between the two groups. This will give a minimum of 99 patients per arm. It is expected that 20% of participants may be lost prior to completing the 3-months and 12-months follow-up assessments so that the final sample would be 120 per arm. A total of N=240 HIV patients with (AUDIT scores 8-19) will be recruited for the study.”

8. Page 8 – more specific detail on the randomisation would be helpful ( example ‘... by checking the random numbers which allocate the case to the intervention arm or control arms’ – not clear what this means).

**Author response:** The randomization process is explained under the heading “Randomization”, also on page 8. The sentence “…by checking the random numbers
which allocate the case to the intervention arm or control arms....” refers to the process described in that section.

9. Missing data – the study will need to have a comprehensive pre-specified Statistical Analysis Plan worked out in advance, and it would seem that missing data (caused by loss to follow up) could be a major methodological challenge given this patient group – couple of points:
   a. The authors state that extensive efforts (‘at least six individual attempts will be made to contact patients by telephone and letter’) will be made to minimise the attrition, which is good to see.
   b. However, ‘observations with a single follow up point missing ... will be imputed from available follow up’ and ‘data for participants who are lost to follow up at 3 and 12 months will be imputed using baseline values’ looks possibly too simplistic – what about multiple imputation (for missing at random) or even looking at modelling missing data mechanisms assumed to be non-ignorable?

   **Author response:** we agree with the reviewer to analyse missing data in more detail. We agree to include multiple imputation in the analysis. An additional text was added in the manuscript under the “Data analysis” heading on page 13: “To avoid possible bias from excluding patients with missing values, patterns of missing values will be analysed. Multiple imputation methods, using generalized estimating equating methods, based on all the data available in the model, using 5 imputed datasets, will be used to impute missing data at all contact points (baseline and follow ups at 3 and 12 months).”

10. Page 13 ‘Trial status – Patients are currently recruited for the trial’ – be more specific i.e. are you saying recruitment is complete?

   **Author response:** The sentence about the trial status has been rewritten to “Patients are currently being recruited for the trial.”

Sincerely,
Diana Huis in ‘t Veld