Supplementary Online Content 2

Chibanda D, Weiss HA, Verhey R, et al. Effect of a primary care–based psychological intervention on symptoms of common mental disorders in Zimbabwe: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.19102

Analytical Plan

May 18th 2015

FRIENDSHIP BENCH ANALYTICAL PLAN
Version 1.0

This plan details the procedures that will be followed for the analysis of data from the Friendship Bench cluster randomised controlled trial.

1. Background

1.1. Objectives

Assess the effectiveness of a problem solving therapy package delivered by lay health workers in reducing severity of common mental disorders, using a cluster randomised controlled trial.

1.2. Setting

Public primary care clinics in Harare, Zimbabwe.

1.3. Trial design

The design is a cluster randomised trial with 6 months of follow-up. Clusters are primary care clinics in Harare. Each clinic provides primary care to between 20,000 and 80,000 people.

The intervention consists of 6 weekly sessions of a problem solving therapy package delivered on a bench in a discreet area outside the clinic, by a lay health worker. The psychological approach is based on providing psycho-education (information, advice and support) together with a problem-solving module that includes a component of positive activity scheduling (behavioural activation). In addition, patients will receive up to 6 brief text messages and/or calls reinforcing the PST approach and encouraging adherence to treatment. After a minimum of 4 sessions participants may choose to participate in an income generating component which focuses on learning a skill and group peer support.

The control arm participants will receive enhanced usual care: usual care from the clinic, medication if indicated, and 2-3 supportive text messages or phone calls with the last message or call being a reminder to attend the 6 month assessment.

1.4. Study population

The study population consists of adults registered at one of the 24 study clinics who attended the clinic during the trial period.

1.4.1. Inclusion criteria

The inclusion criteria are the participants must be

- Aged 18 and over
- Having a score of 9 or above (out of 14) on the SSQ-14 at enrolment
- Able to give informed consent

1.4.2. Exclusion criteria

Participants will be excluded if any of the following apply;

- Residing outside the clinic catchment area
- Address cannot be verified through the clinic registry
- Unable to comprehend the nature of the study
- Reported physically unwell by the clinic nurse-in-charge
- Suicidal intent
- End stage AIDS
- Currently in psychiatric care
- Third trimester of pregnancy
- Less than three months post-delivery

2. Trial endpoints

2.1. Primary endpoint

The primary outcome measure is SSQ score and the endpoint is 6 months after trial enrolment. All study participants will be contacted to remind them to attend the clinic for a 6 month visit. SSQ score is a continuous outcome ranging from 0 to 14 and will be reported as a cluster-level mean and standard deviation.

2.2. Secondary endpoints

The secondary outcome is depression as defined by the PHQ-9 and the endpoint is 6 months after trial enrolment. Depression is a binary variable defined as PHQ-9>11 and the DSM algorithm for major depressive syndrome (PHQ1 or PHQ2 and five or more of PHQ1-PHQ9 are least "More than half the days" (PHQ9 is counted if present at all). These will be reported as a cluster-level percentage prevalence.

3. Methodology

3.1. Sample size

24 clinics were randomised in a 1:1 ratio, 12 to the intervention arm and 12 to the control arm. Each clinic enrolled 24 patients, making 576 participants in total. The sample size of 24 clusters, each with 24 participants provides 80% power to detect an effect size of 0.75, assuming a coefficient of variation (k)=0.2. We would have 90% power to detect this effect size if the coefficient of variation is smaller (k=0.16), and 90% power to detect a larger effect size of 0.85 if k=0.19.

3.2. Randomisation

The 24 clinics were stratified into 5 strata, defined on number of registered patients, number of staff, gender ratio of registered patients and HIV prevalence within the clinic population. The number of clinics per stratum was 2, 2, 6, 6 and 8. A restricted randomisation approach was used. 3268 allocations were selected which met the criteria of equal distribution of strata within trial arms. Of these 3268 allocations, one was selected at random in a public randomization ceremony held on February 12th 2014.

3.3. Data management

Data collection is done at the individual level using tablets. Data collection is at two timepoints: enrolment, and 6 months after enrolment. Data will be exported to Stata 13.0 for analysis.

4. Analysis methods

Analysis will be carried out using Stata 13.0.

Due to the relatively small number of clusters, analyses will be based on cluster-level summary measures, as individual-level regression methods do not perform robustly when there are relatively few clusters per arm, especially for stratified cluster randomized trials.

The primary analysis of primary and secondary endpoints will be by intention to treat, adjusted for baseline imbalance as appropriate. Further secondary analyses will include stratified analyses by HIV status, gender, poverty level and baseline depression severity, and per-protocol analyses by adherence to the intervention(section 4.4).

4.1. Preliminary descriptive analysis

Descriptive analysis will be conducted at the individual level. The number of patients screened, the number eligible, the number who agree to participate and the number who complete outcome assessments will be reported in a CONSORT chart. Reasons for non-eligibility and failure to complete outcome assessments will be reported.

Baseline comparability will be assessed for individuals who did not consent to be part of the trial, and of participants who did not complete outcome assessments. Comparability of participants in the two arms will be assessed for potential confounding factors: age, sex, HIV status, education level, income, marital status, religion, WHO disability score, red flag for suicidality (SSQ score>11 with an answer 'yes' to question 11) and baseline SSQ score. Significance tests will not be conducted, as any differences between arms must be due to chance.

4.2. Primary endpoint

The primary endpoint is SSQ score at the 6 month visit. The mean SSQ score for each cluster will be calculated and shown by strata and arm. The arithmetic mean and SD of these mean scores and associated 95%CI will be estimated by arm. Linear regression of the mean score using 2-way analysis of variance (ANOVA) on arm and strata will be used to estimate the difference in SSQ score and 95%CI associated with the intervention. This method gives equal weight to each cluster.

The adjusted mean difference will be calculated using a two-stage process. Firstly, a linear regression model will be fitted on the mean SSQ score, including terms for the adjustment factors (e.g. HIV, gender, baseline severity), but not study arm. The fitted model will be used to obtain the cluster-level difference-residual (observed-expected mean SSQ score). Linear regression of the cluster-level difference residuals on strata and arm (including an interaction term) will then be used to estimate the adjusted risk difference and the corresponding 95% CI will be calculated from this variance, using a t-statistic with 14 df.

4.3. Secondary endpoint

The secondary endpoint is the proportion of participants with depression within a cluster. The prevalence of depression within each cluster will be calculated, and shown by strata and arm, and a log transformation will be applied to control for skewness. The mean and SD of the log risk of depression by cluster will be used to estimate the geometric mean and associated 95%CI for each arm of the study. Linear regression of the mean log risk on strata and arm will be used to estimate the risk ratio between arms and 95%CI. The approximate variance for the mean risks in each arm will be obtained based on the residual mean square from a 2-way ANOVA on arm and strata. A 95%CI for this will be calculated from the variance using a t-statistic with 14 degrees of freedom.

Adjusted RRs will be calculated by using logistic regression to adjust for confounders at the individual level. The regression model included terms for the adjustment factors (e.g. HIV, gender, baseline severity), but not study arm. For each cluster, the fitted model will be used to obtain the ratio of observed to expected (O/E) events. Linear regression of the ln mean O/E on strata and arm (including an interaction term) will be used to estimate the adjusted RR and the corresponding 95% CI was calculated from this variance, using a t-statistic with 14 df.

4.4. Tertiary endpoints

We will include the following as tertiary endpoints

- GAD7 (cut-off score 10)
- WHO-DAS score (continuous)
- EQ5 score (binary)
- AUDIT score (cut-off score 8)

4.5. Secondary analyses

Further analyses will be conducted on both the primary and secondary endpoints as follows:

1) Stratification by HIV status, gender and baseline severity

2) Per-protocol analyses excluding intervention participants who received fewer than X sessions

3) Sensitivity analyses excluding participants seen outside a 3 week window around the 6 month visit date

Table 1: Baseline characteristics: assess representativeness of study participants

		Eligible but did not consent	Enrolled in trial	Completed outcome assessment	Did not complete outcome assessment
N			576		
Sex	% female				
Age	Mean, sd				
HIV status	% positive				
SSQ-14	Mean, sd				
Depression in patients with SSQ>11	% depressed	-			
Education	Primary not completed Primary completed >=Secondary				
Marital status	Single Married Widowed/divorced				
Religion	Christian Other				
WHO DAS score	<10 10-20 >=20				
GAD-7	<10 >=10				
Red flag	% yes				

Table 2: Baseline characteristics by arm

		Intervention arm	Control arm	Intervention arm and completed outcome assessment	Control arm and completed outcome assessment
		N=288	N=288		
Sex	% female				
Age	Mean, sd				
HIV status	% positive				
SSQ-14	Mean, sd				
Depression in patients with SSQ>11	% depressed				
Education	Primary or less Primary completed >=secondary				
Marital status	Single Married Widowed/ divorced				
Religion	Christian Other				
WHO DAS score	<20 >=20				
GAD-7	<10 >=10				
Red flag	% yes				

Table 3: Impact of intervention on depression severity and prevalence

Outcome		Intervention arm	Control arm
		N=12	N=12
SSQ-14	Baseline SSQ-14		
	Arithmetic mean (95% CI), sd		
	Unadjusted mean difference[1] (95% CI)		
	Adjusted mean difference (95%CI) [2]		
Prevalence of depression	Geometric mean prevalence (95%CI)		
	Unadjusted risk ratio[3]		
	Adjusted risk ratio[4]		
	Unadjusted risk difference[5] (95%CI)		
	Adjusted risk difference[6] (95%CI)		

Table 4: Impact of intervention on depression severity and prevalence

Outcome		Intervention arm	Control arm	Effect estimate	Test
		N=12	N=12		
Cluster-mean SSQ-14 at 6 months	Arithmetic mean (95% CI), sd			Mean difference (95% CI)	Linear regression of mean score adjusting for strata
Cluster-level proportion with depression at 6 months	Geometric mean prevalence (95% CI), sd of the log prevalence			Risk ratio (95% CI)	Linear regression of log mean risk adjusting for strata
				Risk difference (95%CI)	Linear regression of mean risk adjusting for strata

[1] Linear regression of mean score adjusting for strata
[2] Linear regression of mean score adjusting for strata, HIV status, etc
[3] Linear regression of log mean risk adjusting for strata
[4] Linear regression of log mean risk adjusting for strata, adjusting for HIV status, etc
[5] Linear regression of mean risk adjusting for strata
[6] Linear regression of mean risk adjusting for strata

Table 4: Process indicators (from the MANAS trial – needs to be adapted)

Process indicator	Original benchmark	Trial result
Proportion of patients who receive at least first psychoeducation session	Minimum 90%	95%
Proportion of moderate-severe cases who receive antidepressants	Minimum 80%	83%
Proportion of all patients who receive ADT	NA	48%
Proportion of patients receiving antidepressants who complete at least 3 months treatment	Minimum 50%	53%
Proportion of moderate-severe cases who receive IPT	NA	5%
Proportion of patients receiving IPT who complete at least 6 sessions	Minimum 50%	33%
Proportion of patients who had a planned discharge	Minimum 60%	51%
Proportion of patients referred to psychiatrist	Maximum 5%	<1%

Table 5: Mean SSQ score and % with depression by cluster

Arm	Cluster	Number of participants	Mean SSQ score	% with PHQ>9
Intervention				
Intervention				
Intervention				
Intervention				
Intervention				
Intervention				
Intervention				
Intervention				
Intervention				
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