Design and Conduct of Randomised Controlled Trials (Part II)

STATS 773: DESIGN AND ANALYSIS OF CLINICAL TRIALS

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Department of Statistics

May 9th 2012, Wednesday, 08:30-10:00
More on Sample Size

• The following questions should be clarified before carrying out a sample size calculation:
  – Study design
    • Parallel, cross-over, factorial, cluster?
  – Primary objective and outcome
    • Variable definition: post-measure, or change from baseline?
    • Type of measurement: continuous, binary, or time to event?
  – Data collection and planned analysis
    • Repeated measures?
    • Simple test, or covariate-adjusted?
    • Test for equality, non-inferiority, superiority, or equivalence?
Hypothesis Tests

- **Equality** (Test drug vs. Placebo)
  \[ H_0 : \mu_T = \mu_P \quad \text{versus} \quad H_a : \mu_T \neq \mu_P, \]

- **Superiority** (Test drug vs. Standard therapy)
  \[ H_0 : \mu_T - \mu_S \leq \delta \quad \text{versus} \quad H_a : \mu_T - \mu_S > \delta. \]
  \( \delta = 0 \)

- **Non-Inferiority** (Standard therapy vs. Test drug)
  \[ H_0 : \mu_S - \mu_T \geq \delta \quad \text{versus} \quad H_a : \mu_S - \mu_T < \delta, \]
  \( \delta > 0 \)

- **Equivalence** (Test drug vs. Standard therapy)
  \[ H_0 : |\mu_T - \mu_S| \geq \delta \quad \text{versus} \quad H_a : |\mu_T - \mu_S| < \delta. \]
Hypothesis Tests

• Superiority Test
  – Equivalent to a one-sided test on Equality
  – The true research assumption in most clinical trials

• Non-Inferiority Test
  – Defines a NI margin with an upper bound
  – Needs a better study design to avoid measurement error and potential bias

• Equivalence Test
  – Mostly for bioequivalence trials that aim to compare a generic drug with the original commercial drug
  – Not appropriate for therapeutic trials
Superiority, Equivalence, and Non-Inferiority Trials

Emmanuel Lesaffre, Dr.Sc.

Figure 1 Superiority, equivalence, and non-inferiority concepts.
A Standard Setting

• Design
  – Two-arm, parallel, individual randomised controlled trial

• Primary outcome
  – Continuous variable, e.g. change in BP
  – Comparison of means between groups

• Data collection and analysis
  – Baseline and post-intervention measures
  – Simple two-group test (two-sided)
  – Equality: $H_0 : \mu_T = \mu_P$ versus $H_a : \mu_T \neq \mu_P$. 
Continuous Outcome

- Study power \((1-\beta)\)
- Level of significance \((\alpha)\)
- Variability of primary outcome \((SD = \sigma)\)
  - Generally assume the same for both groups
- Size of treatment effect \((\Delta)\)
- Sample size required per arm
  - Most efficient with equal treatment allocation (i.e. \(n=n_1=n_2\))
  - Unequal group sizes \((n_1 = kn_2)\)

\[
n_2 = \frac{k + 1}{k} \left( z_{(1-\alpha/2)} - z_\beta \right)^2 \sigma^2 \frac{\Delta^2}{\Delta^2}
\]
Z-score for $\alpha$ and $\beta$

- $Z \sim \text{Normal (0, 1)}$
- Bell-Shaped density (total area under curve = 1)
- $Z_{1-\alpha/2} = z$-quantile from where the upper area under curve = $\alpha/2$
- $Z_\beta = z$-quantile from where the lower area under curve = $\beta$
- Most software can do the calculation
The Z-score Table

- With a fixed size of treatment effect and variability of the primary outcome, the term \( (z_{(1-\alpha/2)} - z_\beta)^2 \) reflects the scale of change in power when the sample size changes.

\[
n = (z_{(1-\alpha/2)} - z_\beta)^2 \frac{2\sigma^2}{\Delta^2}
\]

<table>
<thead>
<tr>
<th>((Z_{1-\alpha/2} - Z_\beta)^2)</th>
<th>5%</th>
<th>1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td></td>
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<tr>
<td>95%</td>
<td>12.99</td>
<td>17.81</td>
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<tr>
<td>90%</td>
<td>10.51</td>
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<td>80%</td>
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<td>11.68</td>
</tr>
<tr>
<td>75%</td>
<td>6.94</td>
<td>10.56</td>
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</tbody>
</table>
Binary Outcome

- Study power (1-β)
- Level of significance (α)
- Control event rate (p₀)
- Size of treatment effect (Δ = p₁ - p₀)
  - Related to the target event rate in the intervention group (p₁)
- Sample size required per arm (n)

\[
n = \frac{(z_{1-\alpha/2} - z_\beta)^2 [p_0 (1 - p_0) + p_1 (1 - p_1)]}{\Delta^2}
\]

\[
\approx \frac{(z_{1-\alpha/2} - z_\beta)^2 [2 \bar{p} (1 - \bar{p})]}{\Delta^2}, \quad \bar{p} = \frac{\text{total events}}{\text{total subjects}}
\]
Time-to-Event Outcome

• In clinical trials the investigator is often interested in a specific event, e.g. death (bad) or complete healing (good)

• Time-to-event may be of considerable clinical or scientific importance in these studies
  – Also known as survival or failure time
  – Normally treated as continuous measures

• Censoring:
  – Event may not be observed for some patients during the study period
  – Time to event is therefore missing (censoring)
  – Special methods are required (survival analysis)
Kaplan-Meier Survival Curve

- Non-parametric estimate of the survival function $s(t)$
- Take into account the "censored" data
- No information on survival after trial finished

Figure 4: Kaplan-Meier estimators for two groups in table 2
Log-Rank Test

• Non-parametric test comparing differences in the survival experiences of two groups
  – *Null hypothesis*: Survival curves in the two groups are the same
  – Make no assumption about survival distributions
  – Comparing at many time points simultaneously
  – Appropriate to use with censored data

• The difference between two survival curves can be summarised by the hazard ratio
Cox Proportional Hazards

• It assumes that the hazard function $\lambda(t)$ for the survival time $t$ given the predictors, $(x_1, x_2, \ldots, x_k)$, has the following regression model:

$$\log[\frac{\lambda(t \mid X)}{\lambda_0(t)}] = \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

$$\Rightarrow \lambda(t \mid X) = \lambda_0(t)e^{\beta X}$$

where $\lambda_0(t)$ is a fixed baseline hazard function

• The hazard ratio, with 1 unit increase in $x_j$, is defined as $e^{\beta_j}$
Freedman Equation

• Suppose the survival rates in two treatment groups are \( P_1 \) and \( P_2 \) respectively, with

\[
\theta = \log_e(P_1)/\log_e(P_2)
\]

• The total number of events (\( d \)) needed to be observed in the trial is:

\[
d = \left( z_{(1-\alpha/2)} - z_\beta \right)^2 \left( \frac{1 + \theta}{1 - \theta} \right)^2
\]

• The total number of patients required can be estimated by:

\[
N = 2d/(2 - P_1 - P_2)
\]

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Freedman (1982), Statistics in Medicine, 1:121-129
Cox Regression Equation

• We want to test the effect of a specific predictor, \( x_j \), possibly in the presence of other predictors or covariates, on the response variable
  – E.g. treatment vs. control group

• The total number of patients required can be estimated by:

\[
N = \frac{4(z_{(1-\alpha/2)} - z_{\beta})^2}{R[\log(\theta)]^2}
\]

where \( R \) is the overall event rate in all patients
Software for Sample Size

- PASS (Power Analysis and Sample Size)
  http://www.ncss.com/pass.html
- Packages in SAS / STATA / R
- Simulations
Clinical Trial Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

- General information
- Background information
- Trial objectives and purpose
- Trial design
- Selection and withdrawal of subjects
- Treatment of subjects
- Assessment of efficacy
- Assessment of safety
- Statistics
- Direct access to source data/documents
- Quality control and assurance
- Ethics
- Data handling and record keeping
- Financing and insurance
- Publication policy
- Supplements
General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.
HEART: heart exercise and remote technologies: A randomized controlled trial study protocol

Ralph Maddison¹*, Robyn Whittaker¹, Ralph Stewart², Andrew Kerr³, Yannan Jiang¹, Geoffrey Kira¹, Karen H Carter¹ and Leila Pfaeffli¹

Efficacy of an m-health exercise-based cardiac rehabilitation programme

(Trial Registration Number: ACTRN12611000117910)

HEART Study Co-ordinating Centre

Postal address
Clinical Trials Research Unit
School of Population Health
The University of Auckland
Private Bag 92019
Auckland Mail Centre
Auckland 1142
New Zealand
Tel: 64 9 373 7999
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Email: heart@ctru.auckland.ac.nz
Web: www.mobileheart.co.nz

- Steering group committee members
- Study management committee members
- Project coordinator
- Study centers
- Coordinating center staff
- Study center staff
- Project sponsors
- Source of study treatment
- Signature page
Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.
A single-blind randomised controlled non-inferiority clinical trial to evaluate the efficacy and safety of cytisine compared to usual care (NRT plus behavioural support) as a treatment for people who wish to stop smoking

(Trial Registration Number ACTRN12610000590066)

3. Background

3.1 Mortality and morbidity associated with smoking

One in two smokers will die of a smoking-related disease, and half of those who die as a direct consequence of smoking will die in middle age. Stopping smoking at any age has clear health benefits. This fact is recognised in all of New Zealand’s health strategy documents.7 Smokers who stop smoking before the age of 36 have the greatest health gains. However, stopping at any age reduces smoking related risks and increases life expectancy. Effective treatments to aid smoking cessation have clear individual and public health benefits and provide the most efficient use of health care resources at a population level.8

3.2 Current smoking cessation treatments

The most effective smoking cessation treatments typically combine behavioural and pharmacological support. Behavioural support is an important component in any smoking cessation intervention, whether it is face-to-face, by telephone or through the internet, and can help smokers increase the chances of quitting by 2-4%.9-10 Pharmacological treatments such as nicotine replacement therapy (NRT), bupropion, and nortriptyline are also very effective, and approximately double the chances of long-term abstinence.1112 NRT is safe and has few contraindications for use. However, bupropion, an atypical anti-depressant, has a number of contraindications (e.g. any history of seizure disorder or bipolar disorder) and adverse effects that need to be considered before use. Nortriptyline also has a number of common side effects and cautions for use. Varenicline, a nicotine receptor partial agonist, is a new pharmacological intervention which triples the long-term chances of quitting compared to pharmacoologically unassisted attempts.13 Varenicline appears superior to bupropion,14 and has the added benefit of few contraindications and no known clinically significant drug interactions. Of the four main pharmacological treatments available for smoking cessation in New Zealand, only NRT (patch, gum and lozenge), bupropion and nortriptyline are subsidised. Consequently, the cost of the other NRT products and varenicline renders them inaccessible to many smokers. Refer Table 1 for costs, aspirin and NRT from the most socio-economic group in New Zealand who have a three times higher age standardised prevalence of smoking than the highest socio-economic group (prevalence in most deprived = 39% men, 27% women, compared to least deprived = 15% men, 13% women).15

3.3 Progress in reducing smoking prevalence is slow

In 1990, 28% of New Zealand adults (aged 15+ years) smoked daily, with this figure dropping to 25.2% in 1996/7, 23.4% in 2002/3, and 18.7% in 2006/7.16 In Māori there had been no downward trend in smoking prevalence during the 1990s and early 2000s, with 46.0% of Māori adults smoking daily in 1996/7, and 47.2% smoking daily in 2002/3. However, in 2006/7 there was a sharp fall in smoking prevalence in Māori, down to 37.6%.17 The prevalence of Pacific adults who smoked daily decreased from 28.4% in 1996/7 to 24.6% in 2002/2003 before falling again to 20.5% in 2006/7.18 In 2008 the prevalence of daily smokers was 42.8% in Māori and 28.4% in Pacific adults aged 15-64 years.19 Based on the current rate of progress it is estimated that it will take 100 years before the New Zealand adult smoking rates reach 5%, the level of smoking in New Zealand doctors.20 New approaches to assist smokers to quit are still urgently needed, ideally ones that are cheap, easily accessible, and acceptable to lower socio-economic groups and especially Māori. One such approach is cytisine since it is non-addictive and does not cause sedation or dizziness.

3.4 What is cytisine and how is it thought to work?

Cytisine is an alkaloid found in plants such as Golden Rain (Cytisus Laburnum), which is native to Europe but grows in the southern parts of New Zealand,21 and New Zealand Kowhai (Sophora Tetraptera).22 Cytisine is a quaternary ammonium compound which resembles nicotine in structure.23 Cytisine is structurally similar to nicotine and binds to alpha-4 beta-2 nAChRs, which is thought to be the main receptor that mediates the central effects of nicotine via dopamine release in the nucleus accumbens of the brain. Cytisine is thought to aid smoking cessation by reducing the severity of smoking withdrawal symptoms (via its actions on nAChRs) and by reducing the reward and satisfaction associated with smoking (via its antagonistic properties). The amount of dopamine released with cytisine administration is approximately 40% of that when nicotine is administered.24

3.5 How is cytisine used?

Cytisine is taken orally in tablet form. Tabex® tablets each contain 1.5mg cytisine, and are taken (as currently recommended by the manufacturer) as a tapering dose over a 25 day treatment period: from one tablet every two hours in the first three days, to one tablet every six hours in the last five days of treatment. Contraindications listed by the manufacturer are: advanced arteriosclerosis, some forms of schizophrenia, glaucoma, myasthenia, malignant hypertension, severe cardiovascular disease, and pregnancy. The manufacturer also recommends that cytisine should not be taken by breast-feeding women in case of adverse effects in the infant and should not be used in patients with ‘arterial hypertension’ (although no reason is given for this statement). Caution is also recommended by the manufacturer in smokers who have “ischemic heart disease, heart failure, cerebrovascular lesions, obstructing arterial diseases, hyperthyroidism, diabetes, renal or hepatic failure, and peptic ulcers”. These cautions are theoretical and stated primarily because there is insufficient clinical experience with cytisine administration in smokers with these conditions. Some NRT product licenses have similar cautions, despite their proven safety in tens of thousands of patients over 20 years of use.2728 Cytisine has many favourable characteristics: it does not affect driving ability or machine operation, undergoes minimal metabolism, is readily absorbed in the gastrointestinal tract, and is excreted by the kidneys.29 There are also no known clinically significant drug interactions.28 The above properties are similar to those of varenicline.

3.6 Is cytisine efficacious?

Although cytisine has an established record of use for almost 50 years, there are only limited data from clinical trials to support its use. As a first step to assessing efficacy, information from placebo-controlled trials is required, using the dosing regime currently recommended by the manufacturer. A recent systematic review of the efficacy and safety of cytisine identified three placebo-controlled trials of cytisine efficacy, (all which used Tabex®) all were published in non-peer-reviewed journals and were conducted over 50 years ago in Eastern Europe prior to the advent of good clinical practice (GCP) guidelines. Assessment of the quality of the trials gives cause for concern. Only one trial clearly stated that randomisation occurred,15 only two used double-blind,15,16 the trials had different treatment durations (17 to 21 days...
Trial Objectives and Purposes

A detailed description of the objectives and purposes of the trial

HEART

5. Study Objectives

The primary objective is to determine the efficacy of an m-health delivered exercise-based CR programme to increase exercise capacity and physical activity compared with usual care (exercise advice and an offer to participate in a cardiac club) in New Zealand adults with a diagnosis of cardiovascular disease.

The secondary objective is to compare the effect of an m-health delivered exercise-based CR programme to usual CR on physical activity, cardiovascular risk factors (hypertension), health related quality of life and cost effectiveness.

5.1 Hypotheses

The primary hypothesis is that an m-health delivered exercise-based CR programme will result in greater exercise capacity at 24 weeks compared to usual care.

5.2 Secondary hypotheses are:

1. An m-health CR programme will result in greater levels of exercise and physical activity compared to usual CR
2. Increased exercise levels will be associated with greater improvements in other cardiovascular risk factors (hypertension) and health related quality of life compared to usual CR
3. An m-health CR programme will be cost-effective

CASCAID

5. Study Objectives

The primary aim of this trial is to answer the question “Is cytisine a safe, effective and acceptable treatment to help smokers wanting to quit?” This trial will determine the one month quit rates of smokers receiving cytisine and compare this with the one month quit rates of smokers receiving NRT. This trial will also assess whether cytisine is acceptable to smokers and cost effective. The study has four main hypotheses, namely that:

1. cytisine plus behavioural support is at least as effective as usual care (NRT plus behavioural support) on smoking abstinence at one month;
2. cytisine plus behavioural support is at least as effective as usual care at reducing the severity of withdrawal symptoms;
3. cytisine has no significant side effects
4. cytisine is an acceptable smoking cessation treatment for Māori, Pacific and non-Māori non-Pacific alike.
Trial Design

- Primary and secondary endpoints
- Type of trial to be conducted, with schematic diagram of trial design, procedures and stages
- Randomisation and Blinding
- Trial treatment(s) and the dosage regimen
- Duration of the trial periods
- “Stopping rules” or “discontinuation criteria” for individual subjects
- Accountability procedures for the investigational product(s), including the placebo and comparator, if any
- Maintenance of trial treatment randomisation codes and procedures for breaking codes
- Identification of any data to be recorded directly on CRFs, and to be considered as source data
Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

a) When and how to withdraw subjects from the trial/ investigational product treatment.

b) The type and timing of the data to be collected for withdrawn subjects.

c) Whether and how subjects are to be replaced.

d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.2 Inclusion criteria

Participants will
1. be aged 18 years or more;
2. have a clinically documented diagnosis of ischaemic heart disease (angina, myocardial infarction, revascularisation, including angioplasty, stent or coronary artery bypass graft) within the previous three to twelve months;
3. be current outpatients who are clinically stable;
4. be able to perform exercise;
5. be able to understand and write English;
6. own a mobile phone and have access to the internet.

6.3 Exclusion criteria

Participants will be excluded
1. if they have been admitted to hospital with heart disease within the previous 6 weeks;
2. have terminal cancer;
3. have significant exercise limitations other than CVD, or currently meet the recommendations for regular physical activity (150 min/week moderate intensity activity).

6.8 Withdrawal criteria

Participants will be informed that they may withdraw from the study or from the intervention at any time. Their withdrawal will not affect their participation in usual care. The Investigator may withdraw the participant from the study if they feel it is in their best interest, or the study is terminated.
6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.
Statistical Considerations

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).
HEART Trial – an example

7.1 Sample size
A total of 170 participants (85 per group) will provide 90% power at 5% level of significance (two-sided) to detect a treatment difference of at least 2.5 ml⁻¹.kg⁻¹.min⁻¹ between the two groups, on change in VO₂max from baseline to 24 weeks assuming a standard deviation of 5 ml⁻¹.kg⁻¹.min⁻¹. Recruiting at least 50 Maori participants (25 per arm) will provide 80% power to detect a treatment difference of 4.0 ml⁻¹.kg⁻¹.min⁻¹ between the two groups under the same assumptions.

7.2 Statistical analyses
Statistical analyses will be performed using SAS version 9.2 (SAS Institute Inc. Cary NC) and R version 2.14 (R Foundations for Statistical Computing). All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. Study data collected from CRFs will be entered into an Oracle database at the CTRU and then extracted into SAS for final statistical analysis.

All details will be addressed in statistical analysis plan.

7.2.1 Baseline characteristics
Baseline characteristics will be summarised using descriptive statistics. Continuous variables will be described as numbers of observed and missing values, mean, standard deviation, median, minimum and maximum. Categorical variables will be described as frequencies and percentages. Results will be presented for each of the two treatment arms as well as overall. Since any differences between randomised groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

7.2.2 Treatment effects
Treatment evaluation will be performed on the principle of intention to treat (ITT), using data collected from all randomised participants. Analysis of covariance (ANCOVA) regression model will be used to evaluate the main treatment effect on the primary outcome between the two treatment groups, adjusting for its baseline measure, age, ethnicity and other potential confounding factors (if they are statistically significant at 5% level). A similar approach will be used for other continuous secondary outcome measures. Logistic regression model will be considered for the analysis of a binary outcome (e.g. meeting physical activity recommendations).

7.2.3 Cost analyses
Cost information, including cost of programme, and direct medical costs (including cost of treatment, primary care, secondary care and over-the-counter medications). We will use the EQ5D to obtain a single preference index for calculation of Quality Adjusted Life Year (QALY) to assess cost per QALY for comparison with other cessation programmes.

7.2.4 Procedures to account for missing data
Appropriate imputation method will be pre-specified and employed on the primary outcome with missing data (if any). No imputation will be considered for other secondary outcomes.

7.2.5 Interim analyses
No interim analyses will be undertaken.
Ethnics Approval

• The principles of ICH-GCP indicate that,

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

Ethics approval
Ethical approval for the trial was received from the Northern X Regional Ethics Committee (NTX/10/10/099). Approval was also obtained from the two Metropolitan Hospitals’ respective Ethics Approval Committees.

• Independent Ethics Committee (IEC) is,

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.
National Application Form for Ethical Approval of a Research Project

Health and Disability Ethics Committees

Northern X Regional Ethics Committee
Private Bag 92522
Wellesley Street
Auckland 1141
Phone: (09) 580 9105
Fax: (09) 580 9001
Email: northernx.ethicscommittee@anch.govt.nz

9 November 2011

Re: Ethics ref: NTX/10/10/099 (please quote in all correspondence)
Study title: Efficacy of an m-health exercise-based cardiac rehabilitation programme: heart exercise and remote technologies (HEART study): Protocol 15/09/10: ProtAmend V#3, 15/05/11: Prot/Amend V#4, 18/10/11; PIS/Cons V#5, 30/8/11.
Sub-study: Cardiac Rehabilitation: measuring physical activity using a cell phone questionnaire; PIS/Cons V#1, 18/10/11

Investigators: Dr Ralph Maddison, Dr Robyn Whittaker, Associate Professor Ralph Stewart, Dr Andrew Kerr, Dr Geoff Kira, Dr Yannan Jiang

We are in receipt of Karen’s letter on 7 November 2011 with amendments to the study.

The protocol amendment and documentation were reviewed by the Chairperson of the Northern X Regional Ethics Committee under delegated authority.

Ethical approval is granted to:
- HEART Protocol Amendment number [version 4, dated 18/10/11]
- HEART Sub-study Information sheet/Consent form version [1, dated 18/10/11]
- HEART Sub-study Flyer [version 1, dated 03/11/11]
- HEART Sub-study Questionnaire - International Physical Activity Questionnaire
Data Handling & Record Keeping

• Data collected from trial participants are normally recorded on Case Record Forms (CRFs) at scheduled visits

• Standard procedures are required to:
  – Design and pilot the CRFs before the study starts
  – Enter correct data in paper and/or electronic forms
  – Quality assurance and data monitoring!
Study Case Record Forms

6.9.1 Case Record Forms (CRF).

1. Form S, includes the following data: title, name, initials, contact details for scheduling appointments, age, gender. Inclusion/exclusion criteria.

2. Form A, includes ethnicity. Certain inclusion/exclusion criteria are confirmed.

3. Form B, includes the following demographic data: occupation, income level, level of education. Medical condition and current medication will be recorded.

4. Form C, will record feedback post programme.

5. Form P, records physiological measures taken at the assessment.

6. Physical activity levels (Form E) will be assessed using the International Physical Activity Questionnaire (IPAQ), a reliable and validated 7-day recall measure which provides a comprehensive evaluation of daily physical activities and assesses the time spent walking, doing light, moderate, and vigorous-intensity activities across various domains. It will assess key psychological questions known to relate to physical activity, including self-efficacy (situational self-confidence) to exercise and to overcome barriers to exercise and motivation.

7. Health related quality of life (Form H) will be assessed using the standard version of the Short Form SF36 version 1 and EQ-5D. The SF36 measures perceived health across eight domains using a 1-00 scale: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Higher scores reflect better perceived health, with 100 being the best possible score for a domain. EQ-5D is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.

8. Form M will record any medication taken during the study period.

9. Adverse Event will be recorded on Form X.

10. Contact Details will be recorded on Form Z.
Basics in CRF: Identifiers, Signature & Version

Form S: Screening & Registration

6. Signature of Study Researcher

6.01 signature printed name

HEART (Heart Exercise And Remote Technologies) • Form S: Screening & Registration
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Form S vDF01 33
Question Style

• **DO**
  - Use simple language
  - Ask specific questions
  - Specify time points clearly

• **DON’T**
  - Use double negatives
  - Ask compound questions (2 in 1)
  - Ask loaded questions

*CRF content is based on the protocol and statistical analysis plan!!*
A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.
Development of SAP

• Primary responsibility of the project statistician
  – Main, Addendum, Amendment(s)

• A separate document to be completed after finalizing the protocol with pre-planned analyses
  – Should be reviewed by the steering committee
  – Possibly updated as a result of the blind review of the data
  – Only results from analyses envisaged in the protocol and amendments can be regarded as confirmatory

• Principal guide to CRF design, data collection and analysis
SAP Template

- Study title, identifying number, and date
- Names of the author and who have been involved in the discussion of analysis
- Name and title of the person(s) authorized to sign the SAP and addendum/amendment(s)
- Preface and Scope of SAP
- Main sections (see next)
Main Sections

• Key trial information from the protocol
  – Study objectives and outcomes
  – Study design including: eligibility criteria, randomisation, blinding, and sample size
  – Study intervention and follow up schedules
  – Data source and quality assurance

• Variable definitions
  – Full definition of outcome measures and any derived variables

• Statistical analysis methods
  – Full details of the analysis population, efficacy and safety evaluations

• Statistical results and report
  – Listing, table and figure templates
  – Statistical analysis report (a technical report of the trial results)
# STATISTICAL ANALYSIS PLAN

The HEART Study

Efficacy of an mHealth exercise-based cardiac rehabilitation programme

## 9 STATISTICAL ANALYSIS

<table>
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<td>9.2 Participant Disposition</td>
<td>17</td>
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<td>9.3 Demographics and Baselines</td>
<td>18</td>
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<td>9.4 Efficacy Evaluation</td>
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</tr>
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<td>9.4.1 Primary Analysis</td>
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<td>9.4.2 Secondary Analysis</td>
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<td>9.4.3 Sensitivity Analysis</td>
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<td>9.4.4 Sub-Group Analysis</td>
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<td>9.4.5 Interim Analysis</td>
<td>19</td>
</tr>
<tr>
<td>9.5 Safety Evaluation</td>
<td>19</td>
</tr>
<tr>
<td>9.5.1 Definition of AE</td>
<td>19</td>
</tr>
<tr>
<td>9.5.2 Definition of SAE</td>
<td>20</td>
</tr>
<tr>
<td>9.5.3 Incidence of AEs</td>
<td>20</td>
</tr>
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<td>9.6 Post Programme Feedback</td>
<td>20</td>
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</table>

## 10 STATISTICAL RESULTS AND REPORT

<table>
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<tr>
<th>Page</th>
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</thead>
<tbody>
<tr>
<td>21</td>
</tr>
</tbody>
</table>
Statistical Analysis Report

• A technical report of the full trial results
  – Complete statistical reference to the investigators
  – Contributing to Clinical Study Report (CSR)
    • See ICH-E3 “Structure and Content of Clinical Study Reports”
  – A well-presented document with the following attachments:
    • Listing, tables and figures (as in templates)
    • Addendum (for additional exploratory analyses)

• Primary responsibility of the project statistician
Reporting RCT

• The CONSORT statement
  (http://www.consort-statement.org/)
  – CONsolidated Standards Of Reporting Trials
  – Intended to improve the reporting of RCT, enabling readers to understand a trial’s design, conduct, analysis and interpretation, and to assess the validity of its results

• Most up-to-date revision is CONSORT 2010

CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,¹ Douglas G Altman,² David Moher,³ for the CONSORT Group
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(for specific guidance see CONSORT for abstracts^21,25)</td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Ratio, with reasons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important changes to methods after trial commencement (such as eligibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>criteria), with reasons</td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>including how and when they were actually administered</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures,</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Including how and when they were assessed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
</tr>
<tr>
<td>Randomisation</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>size)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numbered containers), describing any steps taken to conceal the sequence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>until interventions were assigned</td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Who assigned participants to interventions</td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants, care providers, those assessing outcomes) and how</td>
</tr>
<tr>
<td></td>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>analyses</td>
</tr>
</tbody>
</table>
# CONSORT checklist

## Results

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
</tr>
<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
</tr>
<tr>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
</tr>
<tr>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
</tr>
<tr>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
</tr>
<tr>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
</tr>
<tr>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
</tr>
<tr>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
</tr>
<tr>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
</tr>
</tbody>
</table>

## Discussion

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
</tr>
<tr>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
</tr>
<tr>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
</tr>
</tbody>
</table>

## Other information

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Registration number and name of trial registry</td>
</tr>
<tr>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
</tr>
<tr>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.*
Participant Flow Diagram

• A diagram showing the flow of participants from enrollment to analysis

• It provides an aid to trialists when writing trial results, and assist readers in the critical appraisal of the internal and external validity of a trial

Value of flow diagrams in reports of randomized controlled trials, Egger et al. 2001 JAMA
CONSORT Criteria

Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)
Summary

• Randomised Controlled Trials (RCTs)
  – Definition:
    • A prospective study to compare one or more intervention techniques against a control group, with the assignment of the participant to a group determined by the formal procedure of randomisation
  – Design of RCT:
    • Parallel, Cross-over, Factorial, Cluster Randomised Trials
    • Randomisation and Blinding
    • Selection of Outcomes and Sample Size Estimation
  – Conduct of RCT:
    • ICH guidelines (http://www.ich.org/products/guidelines.html)
    • Development of study protocol, SAP and SAR
  – Reporting of RCT:
    • The CONSORT statement (http://www.consort-statement.org/)
References

• Fundamentals of clinical trials, 3rd Edition (Friedman et al. 1998)
• Sample size calculations in clinical research (Chow et al. 2003)
• Tables of the number of patients required in clinical trials using the logrank test (Freedman 1982, *Statistics in Medicine*, 1:121-129)
• ICH-E3 (1996): structure and content of clinical study reports
• ICH-E6 (2002): guideline for good clinical practice
• ICH-E9 (2003): statistical principles for clinical trials
• CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials