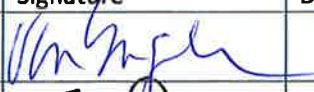
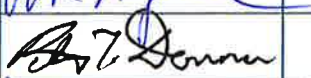
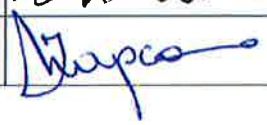
Approved 20/05/2016

Statistical Analysis Plan

TRIAL FULL TITLE	Observational Prolonged Trial in Myotonic Dystrophy type 1 to Improve Quality of Life Standards, a Target Identification Collaboration		
SAP VERSION	V2.0		
ClinicalTrials.gov nr	NCT02118779		
SAP VERSION DATE	20/5/2016		
		Signature	Date
TRIAL CHIEF INVESTIGATOR	Baziel van Engelen		31/5/2016
SAP AUTHOR	Prof Peter Donnan		24/5/16
TRIAL STATISTICIAN, SAP AUTHOR	Adrian Hapca		24/05/16

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1 Abbreviations and Definitions

AE	Adverse event
ADL	Activities of Daily Living
CI	Chief Investigator
CIS	Checklist Individual Strength Fatigue
CBT	Cognitive Behavioural Therapy
CRF	Case Report Form
DM1	Myotonic Dystrophy type1
DM1-Activ	Myotonic Dystrophy type1 Active
DNA	Deoxyribonucleic Acid
FDSS	Fatigue and Daytime Sleepiness Scale
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
InQoL	Individualised Neuromuscular Quality of life Questionnaire
ISF	Investigator Site File
MIRS	Muscular Impairment Rate Scale
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
6MWT	Six Minute Walk Test
TCTU	Tayside Clinical Trials Unit
TRuST	Tayside Randomisation SysTem

2 Introduction

2.1 Preface

Myotonic dystrophy type1 (DM1) is a rare, inherited, chronic progressive disease as well as an autosomal dominant multisystemic disorder. It is the most common adult form of muscular dystrophy, with a prevalence of approximately 10 per 100,000 people affected (Norwood 2009, Norman 1989). With 733 million people in Europe, we estimate that 75,000 people are DM1 patients in Europe (European Commission 2011).

3 Study Objectives and Outcomes

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the effect of a tailored behavioural change intervention comprising CBT and graded exercise on participation (as measured by the DM1-Activ scale) for severely fatigued patients with myotonic dystrophy type 1 compared to standard care.

3.1.2 Secondary Objectives

- Creation and introduction of evidence based clinical guidelines on exercise and cognitive behavioural therapy combined with graded exercise in DM1.
- Identification of biomarker profiles as surrogate outcome measures and moderating or mediating factors of the efficacy and safety of the clinical response.
- Create clinical trial infrastructure for European DM1 trials, including the collection of natural history data from a large cohort of DM1 patients.

3.2 Outcomes

3.2.1 Primary Outcome

- The primary outcome measure will be the DM1-Activ measured at the end of the 10-month intervention period. DM1-Activ is a specific outcome measure of activity and participation for patients with DM1.

3.2.2 Secondary Outcomes

<u>Activity</u>

- 6-minute walk test (6MWT) with BORG Scale assessment (0-10 Rating of Perceived Exertion score)

- Activities of Daily Living (ADL) assessment
- Myotonic Dystrophy Health Index (MDHI) (overall score)
- Physical activity measured with accelerometers, specifically mean (Euclidian norm minus one) ENMO over 24 hours of each day (ENMO24), the most active 5 hours of each 24 hour period (M5mg) and the least active 5 hours of each 24 hour period (L5mg).

Fatigue and sleepiness

- Fatigue and Daytime Sleepiness Scale (FDSS)
- Checklist Individual Strength (CIS) subscale fatigue severity.

Quality of life

- Individualised Neuromuscular Quality of Life Questionnaire (InQoL)

Mood

- Beck Depression Inventory Fast Screen (BDI-FS)

Cognitive

- Apathy evaluation scale (AES) (clinician version)
- Stroop colour word test (Scores recorded as time needed to complete and no. of errors)

3.2.3 Measures used as potential effect modifiers

Extra data were collected to evaluate their potential as modifiers of the effect seen in the trial:

- Muscular impairment rating scale (MIRS)
- McGill pain questionnaire (Pain severity VAS)
- Cognitive behavioural variables (self-efficacy scale for fatigue (SES-28); Jacobsen Fatigue catastrophising scale (FCS); illness management questionnaire (IMQ); Illness acceptance scale; Social support (SSL-D)/Social Support List Interactions (SSL-I)/ Social Support List Negative Interactions (SSL-N))
- Trail making test Part A and B
- Adult Social Behaviour Questionnaire (ASBQ)

4 Study Methods

4.1 General Study Design and Plan

OPTIMISTIC is a two-arm, multi-centre, randomised controlled trial designed to compare cognitive behavioural therapy, plus graded exercise against standard patient management regimes. It is expected that the trial and outcome work will lead to new clinical guidelines for DM1 management. The intervention comprises cognitive behavioural therapy (CBT) and graded exercise therapy, both of which aim to achieve a more active lifestyle.

The effectiveness of this intervention, together with any adverse events associated with it, will be compared to standard patient management. Outcome measures will be measured at baseline (which may be done at screening, or as a separate visit within 5 weeks of screening), 5 months (± 1 month), 10 months (±1 month, the end of the intervention period) and at 6 months (±1 month) post intervention (*i.e*. 16 months from baseline). This SAP covers the analysis up to the 10 months primary outcome measurement point.

The baseline period constitutes either a combined screening/baseline visit if the genetic diagnosis of DM1 is confirmed or a separate screening visit, in which to obtain a blood sample for DM1 genetic status, followed by a baseline visit, if confirmed. Depending upon the medical and DM symptom history obtained from non-confirmed participants, they may carry out all screening and baseline activities while awaiting the genetic confirmation. This will allow those participants to enrol into the screening phase of the study prior to genetic confirmation. It is of the opinion of the specialists that non-confirmation will occur in very few cases.

4.2 Inclusion-Exclusion Criteria and General Study Population

Participants will be recruited from myotonic dystrophy clinics and neuromuscular centres in the UK, the Netherlands, Germany and France. See *5 Sample Size Calculation* for more details with regard to participant numbers.

Participants will be randomised 1: 1 to receive a 10-month tailored behavioural change intervention, or standard care.

4.2.1 INCLUSION CRITERIA

Inclusion criteria are below. Judgements as to whether a potential participant meets an inclusion criterion are made by the treating clinician unless stated otherwise.

1. Able to provide informed consent.
2. Genetically proven DM1, aged 18 years and older, suffering from severe fatigue (CIS-fatigue severity subscale ≥ 35). The genetic diagnosis and level of fatigue will be determined as part of the eligibility screening process.
3. Ability to walk independently (ankle-foot orthoses and canes are accepted).

Carers inclusion criteria involve the ability to give informed consent and to complete study questionnaires.

4.2.2 EXCLUSION CRITERIA

Exclusion criteria are below. Judgements as to whether a potential participant meets an exclusion criterion are made by the treating clinician unless stated otherwise.

1. Neurological or orthopaedic co-morbidity interfering with the interventions or possibly influencing outcomes.
2. Use of psychotropic drugs (except Modafinil, Ritalin and antidepressants where the dosing regimen has been stable for at least 12 months prior to screening). If the doses of Modafinil or

Ritalin increase during the 10 months of intervention/non-intervention then the participant will be excluded.

3. Severe depression at screening as per clinical judgement
4. Participation in another clinical trial of an investigational medicinal product (CTIMP) or other interventional study considered to influence outcomes being evaluated in OPTIMISTIC concurrently or within 30 days prior to screening for entry into this study.
5. Unable to complete study questionnaires.

The exclusion criteria for carers are: the inability to give informed consent, to complete questionnaires and attend CBT sessions with participants.

4.3 Randomisation and Blinding

Randomisation will be via a centrally controlled web-based, GCP-compliant randomisation system, run by Tayside Clinical Trials Unit (TCTU) called TRuST (Tayside Randomisation SysTem).

Randomisation will be:

- stratified by site
- minimised for baseline DM1 severity measured by the Muscular Impairment Rate Scale (MIRS) 5-point scale
- minimised for baseline involvement (or not) of a caregiver

For immediate family member participation TRuST will assign the initial family member as per stratification and minimisation criteria, with subsequent family member(s) being assigned by TRuST into the same group. All participants will be asked for consent to allow the study team enquire if another member of their immediate family is enrolled into OPTIMISTIC. Their name will be required to review the randomisation log to establish their study ID. The study ID of the initial family member will be entered into TRuST thereby allowing same group allocation.

5 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

The sample size is 208.

The primary outcome is the DM1-Activ scale, which is a Rasch-built measure of activity and participation for patients with DM1 and is currently the best such measure for these patients. Based on a minimum clinically important mean difference of 1.4 on the 40-item DM1-Activ scale, standard deviation of 3.5 and effect size = 0.4, 80% power and 5% significance level, we need a sample size of 100 in each arm, or 200 in total. However, DM1 is a genetic condition so it is likely that some members of the same family will take part in the study, which means that there will be some clusters of more than one family individual and the sample size needs to be inflated to account for this. Newcastle estimates that this may affect 50 % of their participants, the other sites estimate that fewer than 10 % of participants will be part of a family group. All sites estimate that almost all family groups will comprise two individuals.

Using estimates of distributions of recruitment across sites (Newcastle = 23 %; Nijmegen = 30 %; Paris = 33 %; and Munich = 13 %) and the above family group proportions gives an average cluster size of 1.17. Using a conservative intra-cluster correlation coefficient of 0.20, gives an inflation factor of 1.035, meaning the sample size is increased to 208, or 104 participants per arm.

This sample size for the primary outcome means that the study is also powered for one of the secondary outcomes, the 6-minute walk test.

6 Proposed Analyses

The primary analyses will be conducted according to the principles of intention to treat as outlined on the ICH E9 'Statistical Principles for Clinical Trials'.

Continuous variables will be summarised by the number of observations, number of missing values, mean, standard deviation, median, inter-quartile range (and range. Summaries will be provided at baseline, at each subsequent time point and for the change from baseline by intervention group. Categorical variables will be summarised by the number of observations, number of missing values and number and percentage in each category. Summaries will be provided at baseline and at each subsequent time point.

The primary outcome and most other outcomes are continuous and so linear models will be utilised and will concentrate on visit 4 at 10 months. The primary outcome of change in DM1-Activ will be analysed using mixed effects (repeated measures) regression models with baseline scores as a covariate. Models will include fixed effects for intervention group, time point, random effects for each subject to account for repeated measures as well as random effects for the correlation within family group. A binary variable will be added to the regression model to represent the difference between the intervention and standard care. The minimisation variables of severity of DM1 (measured using the MIRS 5-point scale) and caregiver involvement at baseline (Yes, No), and age will also be added to the regression model as fixed effects, as well as stratification by site.

Subgroup analyses will be carried out by first testing for a subgroup factor by intervention interaction. If this is significant at the 5% level, results will be estimated separately by the different subgroups.

Subgroup analyses will be implemented for: number of sessions attended (initially as continuous and then explore cut-offs), site, severity of DM1, caregiver (Yes, No), gender, age, those who had CBT compared to those who had CBT plus graded exercise (about a 25% of intervention group received CBT plus graded exercise.

These analyses will also be repeated for all the secondary outcomes listed in 3.2.2 at 10 months.

Appropriate transformations of outcomes will be performed where necessary to satisfy modelling assumptions. Mixed models has the added advantage of dealing with data that is missing at random (MAR) where all data present at each time point is used in the analyses. Analyses will be carried out using SAS 9.3, Cary NC, 2011 software and code will be checked by an independent statistician prior to being run by the trial statistician.