

PROJECT FINAL REPORT

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Final publishable summary report

1 An Executive Summary

OPTIMISTIC, Observational Prolonged Trial In Myotonic dystrophy type 1 to Improve QoL-Standards, a Target Identification Collaboration, ran a 16-month randomized trial to assess the effectiveness of cognitive behavioural therapy with graded exercise on activity and participation in severely fatigued adult Myotonic dystrophy type 1 (DM1) patients with genetically confirmed diagnosis compared to usual care. The trial has ended and the analysis described in its statistical analysis plan is complete. A total of 255 people with myotonic dystrophy type 1 took part from four centres in four countries (France, Germany, the Netherlands and the UK). Our primary outcome was the DM1-activ-c scale measured at 10-months post-randomisation. We also followed participants up for a further six months.

OPTIMISTIC recruited a total of 255 patients, 128 participants were allocated to the intervention arm and 127 to usual care alone. Baseline characteristics in the two groups were similar. In total, 115 participants (89.8%) in the intervention group and 116 participants (91.3%) in the comparison group completed the primary outcome assessment at 10 months. Retention was better (in fact only 1/3 or the expected 30%) than expected and allowed us to reduce our recruitment target while easily achieving our required statistical sample size of 208 participants.

The results are very encouraging and suggest that the OPTIMISTIC intervention provides benefit. At 10 months, participants in the intervention group had improved on not only the DM1-Activ-c scale, our primary outcome, but there were important differences found on other key measures such as the six-minute walk test (6MWT), the fatigue and daytime sleepiness scale (FDSS), checklist individual strength subscale fatigue (CIS-fatigue) and the activity levels (24 hours and most active 5 hours) measured with accelerometry. Participants in the intervention group show an increase in their muscle tissue on quantitative muscle Magnetic resonance (MR) imaging, while the progression of fat remains similar to the control group. The full results will be made public in our main trial publication, which is now in preparation; submission is planned for summer 2017,

We recorded a total of 399 adverse events (AE) with 218 (54.6%) of these related to falls, of which 148 and 70 occurred in the intervention and usual care group, respectively. The number of falls with injury was similar between groups. AEs other than falls were much more evenly distributed between groups. A total of 47 serious adverse events (SAE) occurred during the conduct of the study in a total of 34 participants. Serious adverse events occurred with similar frequency in the intervention group and the comparison group: 24 versus 23 events, respectively. SAE were mostly of cardiac, pulmonary or gastro-intestinal origin. Distribution of SAE across both groups was even, with the exception of SAE related to falls, which occurred more frequent in the intervention group. Six SAE's related to falls were recorded in the intervention groups versus 2 in the usual care group. No adverse events occurring in $\geq 5\%$ other than falls were noted.

Conclusion

These results demonstrate that, as suggested by our previously published disease model, a behavioural change intervention can beneficially affect activity and participation in severely fatigued DM1 patients. Moreover, it has been possible to run a large trial in the European rare disease population, showing that such trials can be done and that sample sizes need not be tiny. The commitment of both participants and site staff to the trial demonstrates the enthusiasm for improving the care of people with DM1 through rigorous evaluations of potential therapies and treatments.

2 A summary description of project context and objectives

Project context of OTIMISTIC:

Myotonic dystrophy type 1 (DM1), a multisystemic and neglected disorder

DM1 is a rare, inherited, 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. With 733 million people in Europe, we estimate that 75.000 people are DM1 patients in Europe (European Commission 2011). Typical symptoms of the disease include progressive muscle weakness and wasting from distal to proximal, ptosis, weakness of facial, jaw and anterior neck muscles, myotonia, daytime sleepiness, fatigue and cataract. Other symptoms of adult DM1 include cardiac conduction defects, as well as endocrine, gastrointestinal and cognitive dysfunction. DM1 is one of the most variable human diseases, has complex, multisystemic and progressively worsening clinical manifestations and leads to severe physical impairment, restricted social participation and premature death (Gagnon 2007; Kierkegaard 2011).

DM1 is a **neglected disease** on various levels. Patients (and their family members) have been suffering from untreated needs due to the heavy burden that DM1 places on not only patients but female partners especially (Gagnon 2007). Despite the huge impact of DM1 on daily life, individuals with this condition tend to play down or avoid expressing their problems when attending appointments with health care professionals, meaning health care is fragmented, inadequate or even deficient for many DM1 patients (Gagnon 2007).

The **aim of OPTIMISTIC** was to improve clinical practice in the management of patients with this rare disease for which no dedicated treatment is currently available. To this end OPTIMISTIC investigated a two component tailored behavioural change intervention (graded physical activity (exercise) and cognitive behavioural therapy (CBT)) and evaluated its effectiveness and adverse events, with particular attention given to the definition of appropriate outcome measures and new clinical guidelines for DM1 management (Figure 1). Relevant stakeholders such as national and European patient organisations were engaged and rapid uptake of developed guidelines was ensured by dissemination plans involving these stakeholders as well as the international TREAT-NMD network and other DM1 specific networks (e.g. the Marigold Foundation, Canada; European Neuromuscular Centre-myotonic dystrophy consortium). In addition, OPTIMISTIC would like to be a member of one the working groups of the International Rare Diseases Research Consortium (IRDIRC), recently launched in collaboration between the European Commission and the US National Institutes of Health, whose mission is to coordinate and foster internationally collaborative research on rare diseases.

DM1: the forgotten aspects of an often neglected condition (Hilton-Jones 1997).

The **complexity** of DM1 poses a challenge for patient management as DM1 patient health care is generally fragmented, inadequate or even deficient for many patients (Gagnon 2007). Numerous factors contribute to the current situation of fragmented care: the multisystemic manifestations of DM1 resulting in several disabilities, the low educational level and the low income of patients (Minis 2010) as well as their poor social support network, the variable understanding of DM1 by physicians, a lack of agreed-upon standards of care for patients with DM1, and differences in the types of locally available health resources. Compared to other neuromuscular diseases, persons with DM1 have among the gravest functional disabilities and the greatest dependence on others for activities of daily living. They also have the lowest social participation, most psychosocial problems and poorest psychosocial well-being. Until recently, **DM1 lagged behind** other neuromuscular diseases in level of clinical care, and was a rather neglected disease on various levels (van Engelen 2005) such as clinical research, but especially in everyday clinical practice. Patients with DM1 do not complain because of a combination of factors such as lack of initiative, daytime sleepiness, facial weakness and dysarthria. These chronic patients do not fit into the average medical or neurological practice and so do not get the care they need, they are not assertive clients of the healthcare system. Active and multidisciplinary care is needed for this societal problem. In conclusion, these factors emphasize the strong need to **improve clinical practice** for DM1 patients (Gagnon 2007). In addition, DM1 not only has a huge impact on patients suffering from this disease, but also on their **partners, especially the female partner** with negative psychosocial and socioeconomic consequences (Cup 2011).

- **From this we concluded that there is an urgent need for evidence-based clinical guidelines for a better care of DM1 patients and their partners.**

Progress in basic DM1 research (Mulders 2010, Wheeler 2008).

DM1 is an inherited disorder caused by an expanded CTG repeat that leads to nuclear retention of a mutant RiboNucleic Acid (RNA) and subsequent RNA toxicity – leading to dis-regulated splicing of many genes and ultimately a multisystemic phenotype. About 80 years after the first description of DM1 and almost 20 years after the discovery of the first DM1 mutation, a series of promising strategies for selective elimination or neutralization of toxic transcripts is now emerging. Effective **antisense oligonucleotides (AONs)** and small molecules are in the pipeline of development (e.g. by Prosensa in Europe and ISIS in the USA), but much work still needs to be done. Before we are able to move these potential therapies forward into clinical trials, we

must first identify the appropriate **outcome measures** to be used as markers for therapeutic efficacy. This requires adequate **longitudinal studies** of disease progression (Blonsky 2012). In addition, it will require the identification of molecular disease **biomarkers** that can be used to follow the extent of disease modification with therapeutic intervention. DM1's highly variable and multisystemic character makes it challenging to define the relevant target tissues and to develop reliable biomarkers for clinical trials. To reduce this potential risk OPTIMISTIC investigated biomarkers on multiple levels (serum, urine, DNA, muscle, heart). A second challenge was the absence of a centralized well-coordinated European clinical trial infrastructure for DM1. In conclusion OPTIMISTIC perfectly fitted with the consensus from the **Marigold Therapeutic Strategy Workshop 2010**: "*There was clear consensus from the meeting that an urgent need exists to develop a common basis for patient characterization and efficacy testing, as well as qualification of outcome measures to inform therapeutic development and clinical trials.*" (Blonsky 2012)

- From this we concluded that there is an urgent need for the definition of appropriate outcome measures in DM1.

The first model-based clinical trial in DM1

1. **Improving physical activity, general aspects.** There is no pharmaceutical treatment for causal or symptomatic relief of DM1 core symptoms (with the exception of Modafinil for excessive daytime sleepiness). Thus the aim of treatment is to relieve impairments, reduce limitations and optimize participation. **Physical activity** has been acknowledged as an important factor for health in general. For patients with a slowly progressive neuromuscular disease, such as DM1, there is accumulating evidence for prescribing low-to-moderate-intensity strength and aerobic exercise training, and an active lifestyle. Nevertheless, recent reviews conclude that existing studies are limited in number and quality, and that there is a need for disease-specific, randomized, controlled trials investigating the effect on quality of life. Along these lines, two components may be pursued: **exercise training or graded physical activity** to improve or at least maintain functional capacity and a **cognitive behavioural therapy (CBT)** approach to stimulate an active lifestyle yet avoiding excessive physical strain. Both aim at improving the patient's quality of life. CBT has been found to be effective in reducing fatigue and disabilities in patients with chronic conditions (Gielissen 2006) though its effect in DM1 patients has not been investigated before.
2. **Improving physical activity, DM1-specific aspects.** Apart from these general remarks on improving physical activity, the main rationale for the two component intervention, exercise training with CBT, is based on our DM1-specific model (Kalkman 2007). (**Figure 2**) The DM1-specific model shows that physical activity and experienced fatigue are main determinants of DM1 health status. OPTIMISTIC was the first **model-based clinical trial** in DM1. It evaluated the effect and the maintenance of effects of exercise training with CBT on the reduction of chronic fatigue in patients with DM1. The study provided a unique set of data with which the relationships between outcome measures at all levels of the ICF (International Classification of Functioning, Disability and Health) could be assessed.

A DM1-specific model of health status with a major role of experienced fatigue

It was demonstrated recently by OPTIMISTIC partner 1 that **severe fatigue**, defined as a score equal to or higher than 35 on the subscale fatigue of the Checklist Individual Strength (CIS-fatigue), was reported by around 70% of patients with DM1 (Kalkman 2005). These severely fatigued patients had more problems with physical and social functioning as well as with their mental and general health than similar patients without severe fatigue. They also had more problems with concentration, initiating and planning. As such, **experienced fatigue** should be clearly distinguished from muscle weakness, which is probably the most common and characteristic symptom of DM1. In a longitudinal study, we built a model of perpetuating factors for fatigue in patients with DM1 (**Figure 2**). It appeared that lack of physical activity, sleep disturbances, pain and reduced initiative all contributed to experienced fatigue. In addition, loss of muscle strength and pain contributed to fatigue through a lower level of physical activity. Ultimately, experienced fatigue and physical activity both contributed to the level of **societal participation** (Kalkman 2007). Thus, theoretically, in order to improve societal participation one should improve muscle strength, reduce pain, optimize physical activity and alleviate experienced fatigue. In addition, falling appears to be a major problem among DM1 patients, with DM1 patients stumbling or **falling** about 10 times more often than healthy volunteers. Since fall incidents often lead to fear of falling and avoidance behavior, they have a serious negative impact on physical activity and participation.

The main objectives of OPTIMISTCS were:

1. To **improve clinical practice** of patients suffering from DM1 by studying the outcome of exercise training with cognitive behavioural therapy (CBT) on the quality of life in patients with DM1 (WP 1, 2, 9).
2. To provide **outcome measures** that are relevant for the patients and have a rate of change that is appropriate for a clinical trial timeframe, and identify genetic factors and **potential biomarkers** that correlate with those measures (WP3-8).

3. Address scientific questions about the moderating and/or **mediating factors** of the short-term **efficacy** and maintenance of clinical response, and the short-term and long-term **safety** of the interventions (WP4 - 8).
4. **Disseminate** the extension of knowledge acquired by the proposed studies to patients and their families, to medical professionals (provide and implement evidence-based clinical guidelines for better care of DM1 patients), and to relevant organisations (TREAT-NMD, Marigold, AFM, see *letters of support in DoW Annex 1*), and to the wider neuromuscular community (WP9-11).

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3 A description of the main S&T results/foregrounds

3.1 Summary of the main results/foreground of OPTIMISTIC

- A behavioural change intervention (cognitive behavioural therapy (CBT) and aerobic exercise program of 10 months) can beneficially affect participation, decrease fatigue and improve objectively measured activity in severely fatigued patients suffering from myotonic dystrophy type 1 (DM1). The full results will be made public in our main trial publication.
- We show that it is possible to run a large European trial in a rare disease (DM1 population). In 4 countries with 4 different languages and health care systems we delivered a harmonised CBT and exercise program.
- We created a European infrastructure for DM1 research. A large database, biobank and patient registries are in place.
- With the exception of serious adverse events (SAE) related to falls, occurring more often in the intervention group, SAE's occurred with similar frequency in the intervention group and the comparison group (24 versus 23 events, respectively in 255 patients). They were mostly of cardiac, pulmonary or gastro-intestinal origin.
- Retention, addressed as one of the elements of CBT, was better than reported in the previous exercise trials in myotonic dystrophy type 1 patients. In fact it was only 1/3 of the expected 30%.
- We validated various DM1 specific and general outcome measures in a large international, multicentre DM1 cohort. The DM1-Activ as primary trial outcome showed valid results and a significant change over time during intervention. We found a normal distribution for the various outcome measures: DM1-Activ, Myotonic Dystrophy Health (MDHI)-total score, 6MWT and FDSS fatigue assessment. We demonstrate a linear regression correlation of DM1-Activ with MDHI total score.
- Cardiac parameters changed over the 10 months intervention time providing important information on the natural history of disease progression in addition to the safety of exercise and CBT in this DM1 cohort.

- A number of microRNA and mRNA markers have been identified in DM1 blood samples. Secondary genetic networks have been built in Ingenuity IPA based on the RNA-sequencing data which highlight molecular pathways involved in phagosome processing, leukocyte and lymphocyte adhesion and inflammatory cascades.
- Patients treated with CBT show an increase in their muscle tissue on quantitative muscle MRI, while the progression of fat remains similar to that of the control group. There was a high correlation between the amount of fatty infiltration and functional outcome measures.
- Genetic characteristics of all DM1 patients in OPTIMISTIC are defined. These data have already yielded important insights into disease biology, in particular with respect to the presence and impact of variant DNA repeats (with individuals carrying them having an age at onset delayed by an average of ~12 years relative to that predicted). We have provided additional evidence that the rate of change of the number of DNA repeats through a patient's life impacts directly on disease severity. These data shed further light on the mechanism by which the mutation causes the disease, and highlights the growth in the repeat as a therapeutic target.
- We introduced a stable specification search for longitudinal data (S3L) (Rahmadi & others, 2017a, 2017b) a robust causal modelling method for longitudinal data (like the data from OPTIMISTIC) that is designed to resolve the instability inherent to structure learning and the immense number of possible models. We implemented S3L as a software package in R.
- Details on dissemination activities can be found in WP10 and chapter 4.

3.2 Main results/foreground of the different work package

WP01: Cognitive behavioural therapy

Background

Previous research has shown that severe fatigue is reported by around 70 % of patients with DM1 [1]. These severely fatigued patients have more problems with physical and social functioning as well as with their mental and general health than similar patients without severe fatigue. They also have more problems with concentration and planning. As such, experienced fatigue should be clearly distinguished from muscle weakness, which is probably the most common and characteristic symptom of DM1. Aside from fatigue, a lack of initiative (apathy) is also prevalent in DM1. Furthermore, there is evidence suggesting that patients often have suboptimal interactions with significant others, which further compromises the functioning of DM1 patients. In a longitudinal study, we build a model of perpetuating factors for fatigue in patients with DM1. It appeared that lack of physical activity, sleep disturbances and pain all contributed to experienced fatigue. In addition, loss of muscle strength and pain contributed to fatigue through a lower level of physical activity. Ultimately, experienced fatigue and physical activity both contributed to the level of societal participation [2]. A lack of initiative further increased fatigue, but also had a direct negative effect on the health status of patients. This is also true from the problems in social functioning. Thus, theoretically, in order to improve health status and societal participation one should compensate for a reduced initiative, optimise social interactions and reduce fatigue. The latter can be done by changing the aforementioned fatigue perpetuating factors. It is assumed that CBT will reduce these problems and thus enable DM1 patients to become more active and improving their health status.

Overall Objective

The overall objective of WP1 was:

1. Design and deliver cognitive behavioural therapy (CBT) for patients in DM1 that will improve their health status.
2. Establish the efficacy of CBT in a multicentre, randomised controlled trial in four clinical sites (Nijmegen, Newcastle, Paris and Munich).
3. Determine the intervention fidelity of CBT.
4. Develop a clinical guideline for CBT in DM1

Results

A treatment protocol for CBT was developed at the RUNMC and piloted in DM1 patients in Nijmegen. On the basis of the promising results, a final treatment manual was developed and a workbook for patients written. The intervention was tailored to the needs and characteristics of the patients on the basis of a pre-treatment assessment. In WP1 the assessment battery was developed to determine which treatment modules were applicable for a patient.

CBT was aimed at improving the health status of patient by addressing their chronic fatigue, reduced initiative and problems in the interactions with others. During the development of the CBT it was decided to combine it with Graded Exercise Therapy (GET) in the subgroup of patients who could formulate goals with respect to exercise and was motivated for this additional intervention. In Munich and Paris only CBT was available, in Nijmegen and Newcastle GET was offered as an add-on.

The CBT intervention comprised a maximum of six modules. All patients started with individual goal setting and psycho-education about the role of cognitive-behavioural variables in the disabilities patients' experience. The patient formulates his or her treatment goals in concrete terms and later on in the therapy the goals were realised step by step by the patient. The treatment was tailored to the patient's problems, which of the six modules a patient received was dependent on the scores on measures that have been collected at baseline assessment. The six modules were: 1) Learning to compensate for a reduced initiative; 2) Suboptimal interaction with caregivers. The disabilities associated with DM1 put considerable strain on caregivers and can also lead to negative interactions with the patient. This is addressed in the module; 3) Regulation of the sleep-wake pattern; 4) Reformulation of dysfunctional cognitions with respect to fatigue and/or DM1; 5) Activity regulation and graded activity. At baseline patients will choose an activity programme with the counsellor, either a low intensity, graded physical activity program (mainly walking) or graded activity followed by a graded exercise therapy (GET); 6) Coping with pain with a focus on dysfunctional cognitions with respect to pain.

Some of the modules were developed on the basis of our own model and other studies in DM1, some modules were based on evidence based cognitive behavioural interventions for other chronic medical conditions.

The treatment manual and patient material was translated from Dutch into English, German and French. The next step was the development of a 3-day training program for therapists. In total 12 therapists were trained in the four countries. They received two-weekly supervision from two experienced clinicians from the RUNMC during the study. CBT was successfully delivered according to plan in the four countries. The intervention ran for 10 months but was frontloaded, which meant that the first 4 months can be considered the 'active' phase with the remaining 6 months the 'booster' phase. In this period of 10 months a patient received 10 to 14 sessions; at least 5 of them were face to face sessions. For the other sessions the therapist could decide, dependent on the traveling distance and the mobility of the patient, to use telephone contact or video conferencing as an alternative. In total 128 participants were allocated to the intervention, thirty-three out of the 128 (25.8%) patients also followed the GET program. Intervention fidelity was evaluated and found to be adequate. There were fewer face-to-face sessions than anticipated due to long travelling distances to the clinical sites. Drop-out rates were low, and loss to follow-up lower than anticipated. Preliminary analyses show positive outcomes of the interventions. The health-status of DM1-patients assessed with the DM1-activ was significantly better following CBT compared to care as usual. Following CBT, DM1 patients also reported less fatigue, less sleepiness and were more physically active. There were no effects due to centre on outcome following CBT, indicating that CBT was effective in all four clinical sites. A combination of CBT and GET is associated with better outcomes following treatment.

Conclusions

The study showed that a complex behavioural intervention can be successfully delivered to DM1 patients in four different European countries. The drop-out rate was low and intervention fidelity was adequate. Health-status was significantly better following CBT compared to care as usual. Following CBT patients were less fatigued, reported less sleepiness and were more physically active. Analysis of follow-up data is ongoing and is expected to be available by autumn 2017. On the basis of the findings and experiences of clinicians, a clinical guideline for CBT in DM1 was written, describing the intervention, how to train therapists and how to implement it in clinical practice. The protocol of the study and the description of the intervention have been published [3]. The paper on the outcome is submitted, papers on mediation and treatment integrity are in preparation.

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WP02: Exercise therapy

This report presents the latest results of a sub-analysis of the completed OPTIMISTIC trial in patients with myotonic dystrophy type 1. This sub-study focus on the feasibility of the applied Graded Exercise Therapy offered to a subgroup of patients looking for a further and more structured increment on their physical activity than the one already achieved as part of the core CBT intervention protocol.

Background

Myotonic Dystrophy type 1 (DM1) is a genetic disorder that among the group of inherited neuromuscular disorders prevails in adults, affecting approximately 1 in every 8,000 people [1]. The way this disease presents itself imitates a premature ageing effect. Due to the nature of its mutation, this disease not only affects skeletal muscle but also impacts on eyes, heart and brain, among other systems, which leads to a significant socio-economical and functional impairment [2, 3]. There is no current cure and the only available treatments are symptoms oriented and not available for all patients [4], hence the search for current care alternatives oriented to improve patients' quality of life and reduce disease burden.

Physical activity and exercise on patients with progressive neuromuscular disorders (NMD) that lead to a sedentary life style have been acknowledged as important for health in general [5-7]. Still, patients with NMD are commonly told not to exercise and there is a patients' concern of worsening the disease by exercising. In DM1 there have been trials providing evidence of being safety and tolerable. However, not enough evidence yet to ascertain efficacy or potential benefits [8,9].

The introduction of an exercise therapy to patients with DM1 might face certain barriers previously identified in this cohort such as: lack of energy, lack of motivation, pain, self-consciousness, costs, etc [3]. Hence, when any of these interventions are planned or promoted, these potential barriers should be discussed with the participant and considered individually. Additionally, when promoting physical activity and exercise for people with neuromuscular disorders that manifest with cardiac complications, such as DM1, provision of evidence-based safe and accessible guidelines, on physical activity and structured exercise (including those suitable for delivery outside the healthcare system) are important.

Overall Objective

The present study objectives were to investigate the feasibility and effects of a graded exercise programme combined with cognitive behavioural therapy (CBT) intervention for those participants on the OPTIMISTIC trial randomized to an intervention group that agreed on proceeding for a Graded Exercise Therapy (GET) programme. Study outcomes included six-minute walking test (6MWT) as assessment of walking capacity, habitual physical activity levels assessed by activity monitors (accelerometers), patient-reported outcomes including fatigue and reported motivation and activity levels. All these were considered as part of the overall intervention effectiveness assessment and were measured at each participant's visit [10].

Graded exercise therapy (GET) methodology:

First visit aimed to define: 1) exercise concept definition, 2) GET goals, 3) GET program and 4) identification of any possible barriers. This visit was always face-to-face with a minimum duration of one hour.

Follow-up assessments were allowed to be performed by phone, skype or face-to-face.

Each participant received a GET diary to record: 1) form of exercise recommended and practiced, 2) duration and frequency of training, 3) sessions per week and, 4) either heart rate measurement or the score of perceived exertion (BORG scale). All these will be discussed with the physiotherapist in charge at every follow-up assessment.

Results

Graded exercise therapy (GET) was only implemented in two out the four centres involved in the OPTIMISTIC trial due to differences in healthcare systems and the availability of physiotherapy and experience with aerobic exercise in two of the centres. Of the 128 participants, who were randomized to the intervention arm of the study; 33 participants received a structured GET program (19 in Nijmegen, The Netherlands and 14 in Newcastle, UK). Two of these participants were lost to study follow-up. The most common forms of exercise practiced included structured walking, cycling, swimming and attending a fitness centre (or gym). There were no more adverse events detected on the GET group when compared to the rest of the groups in these sites.

Every follow-up meeting or phone discussion was recorded by the site's physiotherapist leading the module and these results are presented in table 1. All patients had an initial face-to-face appointment with a lead physiotherapist in the neuromuscular field who explained the concept of exercise training and the minimum requirements of this to be considered exercise; differentiating this from graded activity. The visit was followed by the definition of fitness SMART (specific, measurable, realistic, within a time frame) goals such as: "reach 6 minutes of cycling 3 to 5 days a week at an intensity level of 7 within the next month". Follow-up reviews occurred at regular intervals and where applicable, the program was expanded or adjusted (table 1 and table 2).

The outcome measures distribution between sites was tested at baseline with no significant differences detected. Progression over time showed significant improvement in the selected primary reported outcome (Checklist Individual Strength CIS questionnaire – fatigue, motivation, concentration and reported physical activity) and the selected primary clinical outcome measure (6 minutes walking test – 6MWT). These results are presented in table 3 as the whole sample and individually per site. When analysed individually by site, only one site showed significant improvement in the levels of reported motivation, however

this factor disappeared when analysed as a whole cohort. However, when analysed/compared as a subgroup within the main study analysis, there was no added effect of GET in addition to CBT compared to CBT with increased activity at its own.

This overall group's habitual physical activity levels can be corroborated as in increment in activity levels as reported by the ankle-worn activity monitor (accelerometer) as presented in table 4. These results match to the physical activity levels reported by the participant at the CIS score with a statistically high correlation value (0.44 at baseline and 0.55 at follow-up).

Conclusions

Our data support exercise as a safe therapy for patients with DM1. The therapists report patients' reported enjoyment of the added activities and a surprising self-challenging motivation as these patients are usually described as lacking in motivation. The description of the intervention will be published as part of the overall intervention manual and the definitive effectiveness (if any) of an added GET will be reported on the main study paper as a sub-group analysis. The outcome measures selected to measure effects on disease burden as reported by patients and as objectively assessed outcomes (6MWT), all showed changes towards improvement after 10 months of intervention follow-up.

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WP 03: Clinical outcome measures, effectiveness and adverse events

Background

Myotonic dystrophy type 1 (DM1) is a multisystemic condition exhibiting highly variable age of onset and severity of symptoms. The resulting heterogeneity of symptoms experienced by DM1 patients creates particular challenges in generating and identifying valid outcome measures suitable for clinical trials. Previous studies used generic measures of quality of life (SF-36), or restricted domains of the disease, including sleep, fatigue (Epworth Sleepiness Scale), and mobility/disability. In addition, most outcome assessments were developed in other even non-neuromuscular populations. The reports of the Outcome Measures in Myotonic Dystrophy Type 1 group of experts (OMMYD-1 and OMMYD-2) highlighted the need for methodologically appropriate outcome measures for DM1 [1,2]. As a consensus, this expert group recommended further research to develop specific outcome assessments validated for use in patients with DM1. Furthermore, longitudinal studies aiming at capturing disease progression changes over time in DM1 patients are scarce [1,2].

In recent years, researchers have developed two DM1 disease-specific patient-reported outcome measures, the DM1-Activ scale [3,4] to assess activities and social participation, and the Myotonic Dystrophy Health Index (MDHI) [5,6] designed to measure patient-perceived disease burden. Regulatory agencies recognize disease-specific patient-reported outcome assessments as acceptable instruments for measuring response to an intervention during clinical trials. While both the DM1-Activ and MDHI measurements intend to be used in clinical trials and for drug labelling purpose, validation data, requested by regulatory agencies, are still limited.

Overall Objective

Therefore, we have taken advantage of the OPTIMISTIC trial to conduct a validation study of the main outcomes used for DM1 in a large international, multicentre DM1 cohort.

The DM1-Activ was designed to investigate daily activities and social participation in patients with DM1. More recently the authors published a revised version of the scale, leading to a final pool of 25 items fitting the Rasch model expectations, named DM1 Activ C, that we used in the Optimistic study [4]. The convergent validity of the DM1 Activ has not previously been assessed. MDHI is a disease-specific measure designed to estimate the overall disease burden and impact of key symptomatic

domains of the DM1 condition. However, more studies are needed to evaluate validation requirements and the responsiveness of this instrument.

Results

Participant's demographic and medical characteristics do not indicate differences across the four clinical sites. We have focused on the distribution of the main outcomes measures across sites and found that with the exception of a higher mean DM1 Activ score at one site, no significant difference was observed for disease burden (MDHI), walking capacities (6 min walk test – 6MWT), pain (McGill pain) and fatigue (FDSS) scores, see table 5.

Further investigation is in progress to address the reason of one higher DM1-Activ score. As the scale is a self-reported measure and considering our prior quality assessment procedure, the current data do not suggest a methodological cause but rather a study site population difference, or cultural difference regarding activities.

Outcome measures show a normal distribution:

To date the distribution of outcome measures values used in DM1 studies is mainly unknown. In the OPTIMISTIC study, the unprecedented number of observations is sufficiently large to address whether outcome measures are normally distributed. Findings from two statistical analysis methods indicate a normal distribution for DM1 Activ values, MDHI-total score, 6MWT distance, and FDSS fatigue. Three MDHI subscales (mobility, pain, and activities) display distributions that are nearly normal. However, the McGill pain questionnaire values are not normally distributed. While a significant proportion of DM1 individuals suffer from pain, the distribution could be explained by a DM1 subgroup not reporting pain. The distributions have been further studied using Q–Q plots (Q: quantiles), a method used to compare the shapes of distributions, providing a graphical view of properties. Similarly, the results confirmed normal distribution for DM1 Activ, MDHI-total score, 6MWT distance, and FDSS.

Outcome measures show a proven validity:

We explored construct validity of assessments, focusing on the two measures having the strongest reliability and validity evidence in literature, by comparing the DM1Activ and MDHI, total and subscores, to various other assessments. Interestingly, this study allowed unique parallel and cross comparative analysis of both measures. Limited concurrent validity data have been reported for the DM1-Activ scale. This measure verified acceptable validity levels when compared to the manual testing (Medical Research Council grading - 0.69) and the muscular impairments rating scale, MIRS - 0.71). We found a linear regression correlation of DM1Activ with MDHI total score ($R^2=0.38$ Slope=-0.61 (+/-0.05), $P<0.0001$). The association increased when comparing DM1Activ with MDHI activities subscore ($R^2=0.52$, Slope=-1.07 (+/-0.06), $P<0.0001$). Both measures demonstrated significant correlation with participants ambulatory functional status, assessed by the 6MWT distance (DM1Activ $R^2=0.41$, Slope=0.09, $P<0.0001$; MDHI, $R^2=0.19$, Slope=-3.09 (+/-0.4), $P<0.0001$). The slope coefficient indicates that DM1 Activ score increases of 0.09 point for every additional meter in total distance.

Longitudinal assessments are under further investigation:

DM1 is a slowly progressive disease and there is limited knowledge on the responsiveness to change of most outcome measures. Long term longitudinal assessment of generic instruments has been reported but the progression of disease-specific measures like the DM1Activ and MDHI scales over time is lacking. Our longitudinal analysis is in progress and will in time help to overcome this important gap in knowledge.

No adverse events in $\geq 5\%$ other than falls occur:

In a total of 255 DM1 patients 47 serious adverse events occurred during the conduct of the study in a total of 34 participants. Serious adverse events occurred with similar frequency in the intervention group and the comparison group. They were mostly cardiac, pulmonary or other origin. Although we recorded a total of 148 falls in the intervention group and 70 in the comparison group, the numbers of falls with injury were similar between groups. Nevertheless, 6 serious events related to falls were recorded in the intervention groups versus 2 in the comparison group were noted. No adverse events occurring in $\geq 5\%$ other than falls were noted.

Conclusions

We substantiated during the OPTIMISTIC trial a validation of outcomes used for DM1 in a large international, multicentre DM1 cohort. The DM1-Activ as primary trial outcome showed valid results and a significant change over time during intervention. We found a normal distribution for DM1 Activ values, MDHI-total score, 6MWT distance, and FDSS fatigue assessment.

We demonstrate a linear regression correlation of DM1Activ with MDHI total score. This relationship is strongly augmented by comparing DM1Activ with MDHI activities sub-score. Both measures demonstrated significant correlation with participant's ambulatory functional status, assessed by the 6MWT distance. Furthermore, the slope coefficient specifies that DM1 Activ

score increases of 0.09 point for every additional meter in total distance. Finally, as interventional related adverse events, no adverse events occurring in $\geq 5\%$ other than falls were noted.

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WP04: Cardiac Investigations

Background

As part of the multimorbidity of Myotonic dystrophy type 1 (DM1) disease, cardiac complications may arise from fatty infiltration in the myocardium, muscle fibres degeneration and fibrosis. These are most commonly manifested as arrhythmias or conduction disruptions and are responsible for the cause of death in approximately 30% of patients with DM1 (Groh, 2008) (Mathieu, 1999) (Petri, 2012).

Cardiac magnetic resonance imaging (CMRI) is an objective and accurate, non-invasive tool that interrogates cardiac structure (volumes and mass), function and assesses for the presence or absence of cardiac fibrosis. A previous CMRI study of 80 DM1 patients (with $>50\%$ manifesting also with significant perceived fatigue); cardiac abnormalities were reported in 44% of participants; including changes not always detectable on electrocardiogram tracings (Hermans, 2012). This protocol was approved by the local Health Research Authority (NRES Committee North East- Tyne & Wear South).

All examinations were performed using the 3.0 T Philips Achieva MRI scanners with a six channel cardiac array (Philips Medical Systems, Best, The Netherlands). During breath holding, a stack of balanced steady-state free precession images were obtained in the short axis view, covering the entire left ventricle.

Using a Viewforum workstation (Philips Medical Systems), the short axis slices at end-diastole and end-systole were used to manually trace endocardial and epicardial borders, with papillary muscles excluded from volume calculations but included in calculations of left ventricular mass. The apical slice was defined as the last slice showing inter-cavity blood pools, and the basal slice as the last slice in which at least 50% of the blood volume was surrounded by myocardium

Overall Objective

This study aimed to accurately detect any hidden abnormalities in a DM1 severely fatigued cohort involved on the main OPTIMISTIC study and assess the safety of the overall intervention that involves increase in physical activity. Additionally, we aimed to analyse the natural progression of the disease with respect to the heart and report a reproducible methodology useful for future clinical trials in DM1.

Results

This CMRI single site-sub study was performed at the UK site: Newcastle upon Tyne Hospitals NHS Foundation Trust and sought to evaluate a cohort of 26 DM1 patients at baseline compared to an age- and gender-matched cohort of 18 healthy volunteers (Table 5).

Study results are summarised in tables 6 and 7; including a summary of the cardiac abnormalities relative to physical activity parameters. Table 6 compares baseline results against accelerometer-reported patterns of physical activity (average – ENMO, maximum levels – M5 ENMO and, low levels – L5 ENMO) and clinical outcomes including 6 minutes walking test (6MWT). Table 7 presents the data of patients who continued standard-care against a study reference that demonstrates cardiac disease progression over time.

Eighteen patients (n=18) underwent pre and post intervention analysis. Mean time between scans was 10 months (+2 months). MR analysis included structure, systolic function, diastolic function, torsion and fibrosis by MRI specialists blinded to the patients' allocated treatment group and/or clinical characteristics. Cardiac parameter changes over the intervening time provide

important information on the natural history of disease progression in addition to the safety of exercise in this patient cohort (Table 8). The final results report will be published following the main study's paper (prior to December 2017).

Conclusions

Preliminary conclusions from these results are as follows:

- 1) These findings suggest that torsion (epicardial dysfunction) is contributing to reduced ejection fraction in DM1 patients and can become an outcome measure to assess heart function in these patients.
- 2) There is a potential natural deterioration of Cardiac Index detectable at 10 months of follow-up that could be investigated further.
- 3) Higher levels of daily life activity correlate to signs of healthier hearts.

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WP5 Biomarkers and bioinformatics

Background

Although the molecular mechanism(s) by which the mutant mRNA results in the DM1 phenotype is not fully understood, recent findings suggest that anomalous RNA–protein interactions have downstream consequences that result in the expression of the DM1 phenotype. Impaired function and localization of alternative splicing regulators contributes to DM1 pathogenesis, and dysregulated alternative mRNA splicing for the insulin receptor, muscle chloride channel and cardiac troponin T protein have been reported. The disturbance of intracellular calcium (Ca²⁺) homeostasis in DM1 muscle has also been implicated as has disruption of microRNA expression in several myopathies. The mRNA splicing of two major sarcoplasmic reticulum (SR) proteins, RyR1 and SERCA1 and their associated microRNAs may play a role in intracellular Ca²⁺ dysregulation in DM1. Here we will take a hypothesis free approach to characterize these and other mRNA targets. By analysing the expression of candidate microRNAs (miRs) relevant to the insulin receptor, muscle chloride channel, SERCA1, RyR1 and troponin T in blood samples from DM1 patients, we seek to validate these mechanisms and examine others. Particularly attention will be also be paid to miR-1, miR-133b, miR-29 and miR-206 which are expressed in both skeletal and cardiac muscle and have been reported to be dysregulated in DM1. Impaired miR-1 processing in particular has been associated with the heart defects in DM1.

Overall Objective

Characterise the mRNA and microRNA gene expression profile in blood samples from DM1 associated with (i) increased disease severity (as noted by clinical MIRS scores) and (ii) increased modal DNA repeat length expansion of the DMPK gene.

Results

mRNA sequencing results:

Top ranked differences in mRNA expression associated with an **increase in disease (MIRS) severity**.

- Differentially expressed genes detected by at least two methods, 441 genes show changes in expression. These reflect the comparison of samples which have the same repeat length but an increased severity (MIRS).
- Data was processed in Ingenuity IPA to ascertain canonical pathways and effect networks associated with disease severity studied in the comparison of Group 2 vs group 1. (see table 9 and 10)

Top ranked differences in mRNA expression associated with an **increase in modal DNA repeat length with high disease severity (MIRS scores 3-4)**

- Differentially expressed genes detected by at least two methods, 217 genes show changes in expression between samples that have the same disease severity but an increased modal DNA repeat length.
- Data was processed in Ingenuity IPA to ascertain physiological functions associated with increased modal DNA repeat length. (see table 11)

With regards to differential microRNA expression in blood, disease severity was associated with 53 miRs while DNA repeat length expansion was associated with 34 differentially expressed miRs. Of the 4 candidate miRs detailed in the grant application (miR-1, miR-133b, miR-29 and miR-206), only miR-29a was found to be validated.

Conclusions

A number of microRNA and mRNA markers have been identified in DM1 blood samples. qPCR validation in blood is underway. In terms of the microRNA regulation of mRNA targets, microRNAs acting on mRNA substrates have been cross-validated to determine which microRNA have a higher rank if they act on one or more of also validated mRNA expression markers. A genetic network in skeletal muscle was constructed using mRNA expression data which confirmed a role for calcium signalling. Secondary genetic networks have been built in Ingenuity IPA based on the RNA-sequencing data which highlight molecular pathways involved in phagosome processing, leukocyte and lymphocyte adhesion and inflammatory cascades. Further analysis on these novel data is in progress.

WP06 Magnetic Resonance of muscle

Background

Progressive muscle weakness in Myotonic Dystrophy Type (DM1) patients is caused by degeneration of muscle cells, leading to a reduction in muscle volume, i.e. atrophy, and replacement of muscle tissue by fat. Magnetic Resonance Imaging (MRI) is a powerful tool to visualize these two processes [1-3], but more importantly also allows their quantification. Fatty infiltration is quantified as percentage of fat within the muscle (fat fraction) and atrophy by determining the anatomical cross-sectional area of the muscle. Furthermore, the actual part of the muscle that is still able to contract, i.e. contractile cross-sectional area, is quantified by subtracting fat fraction from the cross-sectional area. As quantitative MRI has been found extremely valuable in other muscular dystrophies [4-9] and in monitoring therapeutic interventions it is anticipated that quantitative MRI will also be important in understanding muscle affliction in DM1 and to assess the effect of the cognitive behavioural therapy (CBT) on disease processes in the muscles themselves.

Overall Objective

The aim of WP06 is to use quantitative MRI to evaluate muscles of DM1 patients for disease state at baseline and natural progression over time as well as for the effect of cognitive behavioural therapy (CBT).

Results

We included 33 DM1 patients and 10 healthy controls who underwent an MRI of the lower extremity, of which 27 DM1 patients also underwent a MRI at 10 month follow-up. Of these 27 patients, 13 patients were randomized in the control group and did not receive any treatment, while 14 patients were randomized to the CBT treatment. The MRI outcome measures were fat fraction, cross-sectional area and contractile cross-sectional area. Disease severity was assessed with the muscular impairment rating scale (MIRS), activity with the DM1-activ questionnaire, a six minute walking test (6MWT) and activity scores obtained from an accelerometer worn for 14 days expressed as the activity during the 5 least active and 5 most active hours. Furthermore, fatigue was determined with the Checklist Individual Strength (CIS). From all patients blood samples were drawn to determine CTG repeat length and inherited progenitor allele length. The DM1 patients did not differ from healthy controls in age and sex (Table 12) and disease severity, activity and fatigue, but the CTG repeat length at the beginning of the study was larger in the DM1 controls.

Baseline MRI outcome:

DM1 patients have a significant increase in the amount of fat and reduction in cross-sectional area and contractile cross-sectional area compared to healthy volunteers (Figure 3). The muscles of the DM1 patients in our study vary from no fatty infiltration to almost completely fat infiltrated (Figure 4A/B), with non-fat infiltrated muscles being more prevalent than highly fat infiltrated muscles. Calf muscles are significantly more affected than thigh muscles ($p=0.026$). The gastrocnemius medialis and soleus appear to be the predominantly affected calf muscles, while in the thigh the vastus intermedius is most severely fat infiltrated (Figure 4C/D). There are no significant differences between the DM1 control group and CBT group in MRI outcomes measures at baseline.

Correlation between MRI biomarkers and functionality:

Fat fraction correlated significantly with the six minute walking test. ($p<0.01$; Pearson's $r=-0.55$ and Pearson's $r=0.43$, respectively), see figure 5. Furthermore, the activity in the 5 most active hours also correlated significantly with the fat fraction ($p<0.001$; Pearson's $r=-0.79$, respectively), while no correlation is found with the 5 least active hours.

See table 12, figure 3-5.

Disease progression over 10 months:

The patients undergoing CBT treatment showed a significant increase in DM1-activ, while this tended to decrease in the DM1 control group. All other functional outcome measures showed no change in both the CBT and control group. The percentage of fat within the DM1 muscles increased significantly over 10 months in both control group and CBT group ($1.2\pm 1.2\%$ and $0.9\pm 1.0\%$, respectively; Figure 5). Treatment with CBT results in a significant increase in cross-sectional area, while cross-sectional area tended to decrease in the control group. The difference between the two groups in change in cross-sectional area over 10 months is significant ($-3.5\pm 8.3\text{cm}^2$ vs $4.5\pm 6.3\text{cm}^2$, $p=0.028$). No correlation is observed between the change in MR outcomes measures and functional outcome measures.

Figure 6: A) Both the DM1 patients in the control and CBT group show a significant progression of fatty infiltration over 10 months ($\dagger p<0.05$). B) CBT treatment results in a significant increase in cross-sectional area, this change is significantly different compared to the control group ($* p<0.05$). C). No significant changes are observed in the contractile cross-sectional area.

Conclusions

In this study we used quantitative MRI to evaluate the disease state and natural progression as well as the effect of CBT on muscles in DM1 patients. Our study confirms that DM1 muscles are affected in a specific pattern and show a slow, but significant progression of fat infiltration over 10 months. The correlation of the amount of fatty infiltration and functional outcome measures indicates that severity of fatty infiltration greatly impacts functionality and is associated with activity in daily life. Patients treated with CBT show an increase in their muscle tissue, while the progression of fat remains similar to the control group. This demonstrates us that CBT has a positive effect on DM1 muscles, despite the ongoing degenerative processes in their muscles.

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WP07: Genetic analysis

Background

Myotonic dystrophy type 1 (DM1) is caused by the expansion of a highly unstable repeat of cytosine, thymine and guanine (CTG) nucleotides in the DMPK gene that varies in length from under 40 repeats in the general population to more than 1,000 repeats in the most severely affected individuals (Aslanidis et al., 1992, Brook et al., 1992, Buxton et al., 1992, Fu et al., 1992, Harley et al., 1992, Mahadevan et al., 1992). Once into the expanded disease causing range of greater than 50 repeats, the CTG tract becomes highly unstable and frequently changes in length from one generation to the next (Ashizawa et al., 1992, Brunner et al., 1993, Harley et al., 1993, Lavedan et al., 1993). Intergenerational length changes are highly biased toward expansions, explaining the 20 to 30 years decrease in age at onset per generation frequently observed in this disorder (Höweler et al., 1989).

The expanded CTG is also highly unstable in the tissues of the body in a process that is expansion-biased, age-dependent and tissue-specific (Jansen et al., 1994, Monckton et al., 1995, Wong et al., 1995). Notably the repeat is particularly unstable and grows very large in affected tissues such as muscle (Anvret et al., 1993, Ashizawa et al., 1993, Thornton et al., 1994) and brain (Ishii et al., 1996, Jinnai et al., 2013). These features likely contribute toward the tissue specificity and progressive nature of the symptoms. In addition, these effects have compromised nearly all previous studies relating the number of repeats with the severity of the symptoms as the traditional approach to measuring the number of repeats takes no account of age dependent expansion. Previously, we demonstrated that by using very careful methods (Monckton et al., 1995) we could estimate the

number of repeats that was inherited by each patient and reduce the confounding effects of age at sampling and dramatically improve the ability to predict age at onset (Morales et al., 2012, Morales et al., 2015).

Notably, we were also able to demonstrate that individuals with faster rates of repeat length growth have an earlier age at onset than expected (Morales et al., 2012, Morales et al., 2015). In addition we previously demonstrated that although the majority of patients likely inherit a pure CTG repeat expansion, a subset of patients contain so called variant repeat interruptions within the gene (Musova et al., 2009, Braida et al., 2010). Such variant repeats, have been shown to reduce both genetic instability of the repeat and appear to be associated with less severe symptoms (Musova et al., 2009, Braida et al., 2010, Santoro et al., 2013, Botta et al., 2017).

Overall Objective

In order to provide additional insight into the genetic basis of variability in DM1, we have sought to estimate the number of repeats inherited, identify the presence of variant repeats and define how quickly the number of CTG repeats changes in the blood DNA of participants recruited to OPTIMISTIC and relate these to symptomatic variation.

Results

For each participant, we used sensitive methods (Monckton et al., 1995) to determine the number of CTG repeats inherited, the average number of repeats at recruitment, and where available (71 participants), the average number of repeats at the time of molecular diagnosis. An expanded CTG repeat was readily detected in 241 out of 250 participants using our standard methods. In an additional seven participants, an expanded repeat was only detected after the addition of an additional reagent that facilitates the detection of variant repeats (Braida et al., 2010).

We identified variant repeats within the CTG repeat of 8.4% of participants (21 out of 250). This included one pair of siblings in both of whom we detected variant repeats. Interestingly, we also detected variant repeats in the daughter of an affected father in whom we did not detect variant repeats, consistent with a brand new genetic change generating new variant repeats. Similarly, we also detected variant repeats in only one of a pair of siblings, consistent with either a brand new gain or loss of variant repeats.

As expected (Morales et al., 2012, Morales et al., 2015, Morales et al., 2016), the number of repeats inherited was the major modifier of age at onset. However, the presence of variant repeats was also important and was associated with a later age at onset.

We also measured how much the number of repeats changed during the lifetime of the patient. As expected, this was mostly driven by the number of repeats inherited and age at sampling. The presence or absence of variant repeats was revealed as a highly significant additional parameter. After correcting for the number of repeats inherited and the age of the participant, we revealed that how quickly the number of repeats changes on an individual basis also impacted the severity of the symptoms with individuals with faster expansions having more severe symptoms.

Conclusions

We were able to detect an expanded repeat in all of the participants with DNA samples available, confirming their molecular diagnosis. As also expected, we were able to establish that the number of repeats inherited is a major determinant of age at onset, establishing our test as much more informative than the traditional diagnostic test. However, it is notable that the proportion of variance in age at onset explained was much lower than observed in previous studies (e.g. (Morales et al., 2012)). This is attributable to the eligibility constraints for recruitment to OPTIMISTIC that dictate that participants must have significant fatigue, but nonetheless be ambulatory and competent and motivated to undergo CBT. **Thus OPTIMISTIC has fewer very mildly affected participants with small expansions, and fewer severely affected patients with very large expansions.** Although broader patient groups have greater utility in revealing aspects of underlying biology, understanding the relationship between genetic factors and symptoms, narrower cohorts of DM1 patients will be important for clinical trials such as OPTIMISTIC in which extreme symptoms are less likely to be targeted.

Here, we have provided additional evidence that the rate of change of the number of repeats through a patient's life impacts directly on disease severity. These data shed further light on the mechanism by which the mutation causes the disease, and highlights the growth in the repeat as a therapeutic target.

The presence of variant repeats, clearly has a profound impact on disease severity with individuals carrying them having an age at onset delayed by an average of ~12 years relative to that predicted. Previous estimates for the frequency of such variants in unselected cohorts vary from ~3 to 5% (Musova et al., 2009, Braida et al., 2010, Santoro et al., 2013, Botta et al., 2017). Here, we detected variant repeats in 8.4% of the cohort (21/250). Indeed, this was as high as 13.6% in the Nijmegen sub-cohort (9/66). Although there was one pair of siblings from Nijmegen who shared variant repeats, none of the other participants from any site with variant repeats were known to be related to each other. Thus, chance sampling of one or a few large families with expanded variant repeats does not explain the high frequency of variant repeats observed in the OPTIMISTIC cohort. Therefore,

it is possible that the reduced disease severity observed in carriers of repeat alleles lead to their over-selection in the OPTIMISTIC cohort, conceivably mediated by a reduced neuropsychological impact of the disease and higher motivation amongst this sub-cohort.

In summary, we have defined the genetic characteristics of the patients recruited to the OPTIMISTIC clinical trial. These baseline data have already yielded important insights into disease biology, in particular with respect to the presence and impact of variant repeats. Going forward these data should provide an excellent resource for further investigating the relationship between the genetic data and the progressive muscular and cognitive symptoms that are being measured as part of OPTIMISTIC.

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WP 08: Machine learning

Background

Causal modelling attempts to model the mechanisms by which variables relate and to understand the changes on the model if the mechanisms were manipulated (Spirtes, 2010) by intervention e.g., cognitive behaviour therapy (CBT). Better understanding of the change mechanisms in the intervention may lead to clinical practice improvement. Moreover, a longitudinal study makes it possible to capture change within subjects over time and thus, gives more knowledge to conclude causal relationships (Frees, 2004). As emphasized in (Fitzmaurice, Laird, & Ware, 2012) there is much natural heterogeneity among subjects in terms of how diseases progress that can be explained by the longitudinal study design. Another advantage is that in order to obtain a similar level of statistical power as in cross-sectional studies, fewer subjects in longitudinal studies are required (Hedeker & Gibbons, 2006).

To date, a number of causal modelling methods have been developed for longitudinal data. In general these causal search algorithms are solely based on a single run of model learning which is notoriously unstable: small changes in finite data samples can lead to entirely different inferred structures. This implies that some approaches might not be robust enough to correctly estimate causal models from various data, especially when the data set is noisy or has small sample size.

Overall Objective

To develop a stable specification search for longitudinal data (S3L) and to apply it to OPTIMISTIC (Rahmadi & others, 2017a, 2017b). We intend to engineer a robust causal modelling method for longitudinal data that is designed to resolve the instability inherent to structure learning and the immense number of possible models.

Results

The main results of WP 08 are a causal modelling method and its software implementation as an R package. The method is called stable specification search for cross-sectional data (S3C) and its extension to longitudinal data called S3L. In general, the main objective of S3L is to search robust and parsimonious causal structures over optimal structural equation models (SEMs). The idea is to address the problem of an immense number of possible models in SEM and the instability in model selection, that is, a slight change in data could lead to a completely different optimal model. More specifically, S3L searches for optimal models which are characterized by two conflicting criteria: fit the data well and parsimonious (simple). Following the idea of stability selection, S3L sub-samples the data, and for each data subset, S3L searches for optimal models as described above. S3L then observes the stability of every pair of variables by using some threshold.

S3C/L is implemented as a package “stablespec” in the R language and environment for statistical computing and graphics. Both the executable and the source code are available at the Comprehensive R Archive Network (CRAN) under MIT license. Documentation is provided alongside the package. We also established a github repository to encourage collaborative works to enhance the features of stablespec. Updates of the package have been made regularly to address any problems encountered and to incorporate feedback from users.

S3C has been published (Rahmadi, R., & others. 2017a). A paper about S3L and a paper about the software implementation stablespec are currently being reviewed. Furthermore, a paper about the application of S3L to analyse the change of cognitive behaviour therapy (CBT) for chronic fatigue syndrome is in preparation.

To strengthen our confidence in our emerging techniques for OPTIMISTIC, we did a replication study on data from a population sharing characteristics of the OPTIMISTIC population, particularly the involvement of a CBT intervention. A longitudinal data set of 183 patients with chronic fatigue syndrome who received CBT, a study that has a similar intervention and measures similar variables as the OPTIMISTIC study. In this study we focus on the causal relationships between cognitions and behaviour in the

process of reducing subject's fatigue severity. We therefore include six variables namely fatigue severity, the sense of control over fatigue, focusing on the symptoms, the objective activity of the patient, the subject's perceived activity, and the physical functioning. The data set consists of five time slices where the first and the fifth time slices are the pre- and post-treatment observations, respectively, and the second until the fourth time slices are observations during the treatment. The result shows that during the CBT an increase in sense of control over fatigue, physical functioning, and perceived physical activity, together with a decrease in focusing on symptoms lead to a lower level of fatigue severity. Interestingly, the actual activity seems insufficient to reduce fatigue severity, however, how the patient perceives his own activity does seem to help. Additionally, we also found that, with similar causal effects, all variables (except the subject's perceived activity and fatigue) also cause the change in fatigue indirectly via the perceived activity as an intermediate variable. This suggests that an increase in perceived activity does seem important to explain the change in fatigue. The variables focusing and functioning also appear to be indirect causes of changes in the level of fatigue severity. Overall results are consistent with those of previous relevant studies (Heins, Knoop, Burk, & Bleijenberg, 2013; Vercoulen et al., 1998; Wiborg, Knoop, Frank, & Bleijenberg, 2012).

Conclusions

The results obtained with S3L on CFS and several other real-world data sets have been corroborated by medical experts and are consistent with previous studies. In general we may conclude that S3L is able to robustly estimate the underlying causal mechanisms.

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WP 09: Clinical trial coordination, standardization and training

Background

OPTIMISTIC ran a 16-month randomized trial to assess the effectiveness of cognitive behavioural therapy with graded exercise on activity and participation in severely fatigued adult DM1 patients with genetically confirmed diagnosis compared to usual care. The trial recruited a total of 255 patients: 72 in France, 66 in Germany, 66 in the Netherlands and 53 in the UK. Of these, 128 participants were allocated to the intervention arm and 127 to usual care alone. Baseline characteristics in the two groups were similar (Table 13). In total, 115 participants (89.8%) in the intervention group and 116 participants (91.3%) in the comparison group completed the primary outcome assessment at 10 months. Retention was better than expected and allowed us to reduce our recruitment target while easily achieving our required statistical sample size of 208 participants. The full protocol was published in the journal *Trials* in May 2015: <http://www.trialsjournal.com/content/16/1/224>.

The last participant provided data on 17/10/2016. Data cleaning started in spring 2016 and ran for almost one year (we were still collecting outcome data until October 2016). Cleaning was complete in March 2017 and data-lock was declared on 15/3/2017. The active phase of the trial then ended. Statistical programming was essentially complete before data-lock so analysis began immediately on data-lock. Formal End of Study declarations were sent to ethics committees in April 2017.

Overall Objective

To design, manage and analyse the trial component of OPTIMISTIC in line with Good Clinical Practice, relevant legislation and best scientific practice.

Results

The results are very encouraging. At 10 months, participants in the invention group had improved on not only the DM1-Activ-c scale, our primary outcome, but there were important differences found on other key measures such as the six-minute walk test

(6MWT), the fatigue and daytime sleepiness scale (FDSS), checklist individual strength subscale fatigue (CIS-fatigue) and the activity levels (24 hours and most active 5 hours) measured with accelerometry. The full results will be made public in our main trial publication, which is now in preparation.

Safety and adverse events:

Safety data are shown in Table 14. We recorded a total of 399 adverse events (AE) with 218 (54.6%) of these related to falls, of which 148 and 70 occurred in the intervention and usual care group, respectively. AEs other than falls were much more evenly distributed between groups. Local requirements meant that the Partner 04 APHP recorded falls differently to the other partners (mainly that Partner 04 APHP recorded more minor stumbles and falls). A total of 47 serious adverse events (SAE) occurred during the conduct of the study in a total of 34 participants. Serious adverse events occurred with similar frequency in the intervention group and the comparison group: 24 versus 23 events, respectively. SAE were mostly of cardiac, pulmonary or gastro-intestinal origin. Distribution of SAE across both groups was even, with the exception of SAE related to falls, which occurred more frequent in the intervention group. In three participants, falls were associated with suspected or actual cranial trauma. Six out of a total of 244 (2.7%) falls that were recorded in this study were classified as SAE.

Conclusion

As suggested by our disease model, a behavioural change intervention can beneficially affect activity and participation in severely fatigued DM1 patients.

Moreover, it has been possible to run a large trial in the European myotonic dystrophy population, showing that such trials can be done and that sample sizes need not be tiny. The commitment of both participants and site staff to the trial demonstrates the enthusiasm for improving the care of people with DM1 through rigorous evaluations of potential therapies and treatments.

WP 10: Dissemination, business development and ethics

Background

UNEW, concentris and RUNMC-Pharm have been the main contributors to the dissemination activities described here. However, all partners have been involved in spreading awareness of the project at meetings, conferences and other relevant events, both internally and externally.

Overall Objective

The main objective of WP10 is to communicate and disseminate the aims and outcomes of the OPTIMISTIC project and to maximise these outcomes through valorisation and relevant business opportunities.

Results and Conclusion

A full list of dissemination activities has been submitted with each periodic report. In addition, the main dissemination activities of OPTIMISTIC are summarized in chapter 4.2. Notably the consortium has had a presence at key events including the International Dystrophia Myotonica Consortia (IDMC) in October 2013 (San Sebastian) and June 2015 (Paris). This is the most prestigious event in the myotonic dystrophy field and is attended by 500 experts (clinicians, scientists and industry) and patients and at both of these occasions a number of posters and platform presentations were accepted from the OPTIMISTIC consortium. Furthermore, the consortium is preparing for a strong presence at upcoming IDMC meeting in September 2017 (San Francisco). The nature of the project means that the bulk of the peer reviewed publications and conference proceedings will come after this funding period, at least 20 publications are in the planning stages including all partners and across all work packages. A publication policy is in place to ensure the integrity of the data and maximum impact of results.

These dissemination activities have been successful through the development of a strong identity, which has been used throughout the lifetime of the project. This includes the development of a logo which is clearly visible on the website and on template materials for presentations and posters. The project website itself www.optimistic-dm.eu has been instrumental as a communication tool both through the internal intranet and the external website.

The core activity of OPTIMISTIC has been the randomised trial of CBT and activity in people with DM1. One of the successes of this trial has been the positive experience with the recruitment and retention participants (see WP9). However one factor in this success is the close working relationship of the consortium with the wider neuromuscular community and in particular the TREAT-NMD network. TREAT-NMD have supported the aims and objectives of OPTIMISTIC and have regularly included information on their website (www.treat-nmd.eu), newsletters (April 2012, February 2013, April 2013, October 2013, February 2014, April 2014, October 2014, March 2015, May 2015 and July 2016) and twitter (various time points). The newsletter reaches over 3500 people each month and over 1200 people follow the twitter account (@treat_nmd). This collaboration with TREAT-NMD has helped to accelerate the development of patient registries in myotonic dystrophy; registries and databases at

all clinical sites (Newcastle, Munich, Paris and Nijmegen) were essential to recruitment in this study. To our knowledge this is the first time these registries and databases have been used to recruit to a large clinical study, and in particular the first involvement in a multinational setting. OPTIMISTIC has shown the utility of this type of tool in DM1 research and the impact to both facilitate and accelerate clinical trials.

Communication with the patient cohort involved in the trial was another factor in the high retention figures we experienced. This was complemented by annual electronic newsletters, which were translated into the four languages of the project, English, French, Dutch and German. These newsletters focussed on different aspects of the project, one explaining the intervention (February 2014), the next with a focus on the genetic aspects (February 2015) of the project and the final newsletter explained fatigue and daytime sleepiness (February 2016). An additional newsletter was sent to announce the close of recruitment (May 2015), and acted as an interim study update. These newsletters were all circulated to patients locally electronically or via clinical appointments in addition to being uploaded to the project website and advertised through TREAT-NMD. These newsletters have also been shared with local patient groups and clinical centres for further dissemination.

Further engagement with the myotonic dystrophy community is clear through the OPTIMISTIC external advisory board, which was created at the outset of the project (see table15). The board includes key opinion leaders from the community listed in the table below, bringing together expertise from outside Europe and across disciplines, importantly including the patient representatives. The external advisory board have met by teleconference (March 2014, November 2014, May 2016), and been invited to general assembly and steering committee meetings where appropriate throughout the duration of the project. They have provided crucial advice on the design and set up of the study, and have been instrumental in helping to interpret and contextualise results.

In addition to the advisory board selected patient representatives, listed below, attended the final steering committee meeting held 20th/21st April 2017 in Rotterdam. This allowed the consortium to get a broader input from the patient community, in particular to seek advice on how to maximise the impact of results.

- Jenny Versnel (Muscular Dystrophy UK)
- Michael Walker (Myotonic Dystrophy Campaign)
- Cornelia Dressler (DG Myotone Dystrophie)
- Christian Maiterth (DG Myotone Dystrophie)
- Mark Hees (Spierziekten Nederland Diagnose Werkgroep MD)

Engagement of the wider community with OPTIMISTIC activities was further cemented at the ENMC workshop held 1st/2nd July 2016, in Naarden, the Netherlands. The workshop “Myotonic Dystrophy - Developing a European Consortium for Care and Therapy” was organised by the four clinical leads of OPTIMISTIC (Hanns Lochmüller, Baziel van Engelen, Benedikt Schoser and Guillaume Bassez). The workshop was set up to help build on the work already carried out in OPTIMISTIC and to help identify future goals and importantly future collaboration both with additional partners in Europe but also those from further afield (USA, Canada). The aims included harmonisation of outcome measures and registries and the foundation of a network for trials in DM1 going forward. This provided an opportunity for the preliminary outcomes of OPTIMISTIC to be presented to a range of key opinion leaders and gain input from a broad cross section of experts including patient representation. In addition, the OPTIMISTIC partners present were able to learn from work being carried out elsewhere. A workshop summary is available on the ENMC website (www.enmc.org) and a peer-reviewed publication will be available in the summer 2017. There was consensus across the board that moving forward we should broaden the collaboration across Europe and this could be best achieved through the foundation of a European consortium for clinical trials in DM1.

The workshop described above is one example of interactions with industry, invitations were sent to IONIS Pharmaceuticals (attended) and AMO Pharma). Industry interest in DM1 is still in its infancy; however, the OPTIMISTIC consortium has acknowledged its importance in the landscape. The data collected in OPTIMISTIC will be invaluable to companies as they move forward with drug development plans. The consortium have met with ISIS Pharmaceuticals and Biogen Idec (IDMC Paris 2015) to present the work being carried out by the consortium but no results have been shared at this stage. At this moment, there have been no strategic partnerships set up with industry but it remains an important issue going forward. The consortium will have a unified process for future interactions with industry.

WP 11 Project management

Effective project management is a central element of successful research. This is because large research projects often entail a lot of administrative work which needs to be dealt in an efficient and timely manner. In view of this, the purpose of WP 11 was project management for the OPTIMISTIC project. This WP took care of all administrative and coordinating tasks.

In order to support the Coordinator in monitoring the compliance by beneficiaries with their obligations under the grant agreement, the project management office at concentris routinely monitored the partners' performance based upon the following:

- To ensure that tasks assigned to them were correctly and timely performed.
- Reports were submitted according to the guidelines and on time.
- Funds were used and claimed according to the rules.
- The partners fulfilled their obligations regarding dissemination and funding acknowledgements.
- Any changes to the work plan were communicated to the European Commission (EC) efficiently.
- Compliant to ethical regulations.

The project office acted as a helpdesk for all participants; it was the central node of communication on a day-by-day basis and communicated with the EC on behalf of the Coordinator regarding administrative and managerial issues (i.e. contract, amendment, reporting etc.).

4 The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results

DM1, although a rare disease, is the most common form of muscular dystrophy. It is in fact a multi-system disorder with various impairments, especially in the muscular, respiratory, cardiac, central nervous, endocrine and ocular systems. DM1 is **psychosocially and economically an important disease**, because of its frequency and the devastating effects of the complex clinical manifestations leading to physical impairment, and lower employment and income. The complexity of DM1 poses a challenge for patient management: most DM1 patients and families do not get up to date medical care. Data from OPTIMISTIC will be used for improving clinical practice in the management and health promotion for people with this neglected disease.

The results of OPTIMISTIC are encouraging and suggest that the OPTIMISTIC intervention provides benefit and beneficially affect activity and participation. If these encouraging results are confirmed, the OPTIMISTIC intervention package offers a new treatment option for DM1 people with DM1.

In summary, improved participation by people with DM1 directly influences psychosocial and economic burden for the patients, carers as well as for society at large.

OPTIMISTIC has a large impact by delivering the following:

1. The first trial of this type in Europe/worldwide, one of the largest trials in this rare disease and therefore a major scientific impact in this field;
2. We mitigated the scepticism of the trial community about the ability of DM1 patients to participate in clinical trials, which may lead to more trials in the future.
3. Develop better DM1 treatments;
4. Involving > 250 patients and their families from the start of the project;
5. We strengthened the self esteem of DM1 patients (empower neglected patients) by showing them that their disease deserved a large trial.
6. Involving four major clinical neuromuscular centres in Europe, with a potential to quickly reach 1000 patients to discuss taking part;
7. Training through 20 workshops of 5 therapists / or 5 workshops of 20 therapists up to 100 therapists from all Europe with the use of the new clinical guidelines developed in the project;
8. A coordinated effort with other initiatives on rare diseases in Europe and internationally (IRDiRC, EURORDIS rare diseases Europe, etc);
9. Delivering data to support improved health policy initiatives in DM1 clinical management;
10. A better public awareness of this neglected disease amongst policy makers and the general public.

These concrete performance indicators will lead to the mid-term improvement of the quality of life of the 1000 patients seen by the OPTIMISTIC partners, and outside the project with other clinical centres, with the training of therapists ensuring the rapid adoption of the new guidelines into clinical practice.

4.1 Socio-economic impact and the wider societal implications of OPTIMISTIC

Social and economic impact:

The impact of DM1 is not only a burden on the patients themselves but also their carers, with female partners being particularly affected by the emotional and psychological distress in caring for their DM1 partner (Timman 2010, Cup 2011). This requires extensive social, counselling and psychological support of the family and carer as well as the patient. In particular, there is a high risk of disintegration of the family unit as the disease takes an increasing psychological, financial and emotional toll on the

family coupled to the physical and worsening medical progression of DM1 symptoms over the years. This negative impact on the family and carer often decreases the socioeconomic contribution they can make to society and has a negative outlook for their own health / well-being (Minis 2010).

In terms of the DM1 patient, their own quality of life (QoL) decreases with age with early death commonly occurring by age 55. Taken together, this decreases their own educational and employment prospects / societal contribution leading together with the negative impact on their family / carer to social and financial deprivation (44% live below the poverty line). This ensures that many live (by necessity) in socially and economically deprived areas in which their QoL is decreased further by negative environmental factors (high crime rate, poor access to resources, etc.). It has been estimated that DM1 patients are six times more likely to live in a socioeconomically-disadvantaged area (Veillette 1992). Such patterns of residential segregation impose a double burden on deprived people: they not only have to struggle with many problems arising from their own lack of income but also they have to live with the social effects of residing in a neighbourhood where the majority of their neighbours are also poor (Wilson 1987). Such a phenomenon can play a role in the perpetuation of poverty in DM1 and can contribute to social exclusion and isolation. Residents of extremely poor neighbourhoods often report the absence of regular sources of social support, including a marital partner and close friends. Also, people who receive less social and emotional support from others are more likely to experience less well-being, more depression, and higher levels of disability from chronic diseases (Wilkinson 1998). The perception of negative support and attitude of family and friends is an explanatory factor for the poor level of participation of DM1 patients in work, leisure and mobility.

Coupled to the restricted possibilities available to them, poor mobility, limited social contact and high degrees of isolation / loneliness are common. OPTIMISTIC aims to address this by ensuring the rapid uptake of improved 2012-level healthcare is made available to DM1 patients by facilitating recognition of and improved clinical DM1 management by the implementation of clear clinical guidelines for use in not only the hospital but also in community and home settings via the training of community nurses.

For those DM1 patients with children, those offspring who develop DM1 often develop a more severe form of this disease (which is called anticipation) than their parent with an increased socioeconomic burden throughout successive generations. (Howeler 1989). Therefore, it is essential that results of OPTIMISTIC achieve improvements in public health policy decisions on resources dedicated to DM1 in particular by influencing via patient organisations changes to insurance company remuneration of DM1 healthcare and budgets / policy available within central governmental health services, e.g. UK NHS for DM1 treatment.

In summary, DM1 is **(psycho)socially and economically an important disease**, because of its frequency and the devastating effects of the complex clinical manifestations leading to physical impairment, and lower employment and income, as discussed above.

Data from OPTIMISTIC confirm and expand the already existing knowledge on the social and economic importance of the disease and will be used for improving clinical practice in the management and health promotion for people with this neglected disease. The results of OPTIMISTIC are encouraging and suggest that the OPTIMISTIC intervention provides benefit and will beneficially affect activity and participation in severely fatigued persons with myotonic dystrophy type 1. The improved participation by people with DM1 directly influences psychosocial and economical burden for the patients and their carers, as well as for society at large.

4.2 The main dissemination activities of OPTIMISTIC

See below a summary of the most important dissemination activities:

Posters

Partner 01 RUMC: Quantitative MRI evaluation of fatty infiltration and edema-like lesions in skeletal muscles of Myotonic Dystrophy type 1.

Partner 01 RUMC: Natural disease progression in skeletal muscles of Myotonic Dystrophy Type 1 evaluated using quantitative MRI

Partner 02 UNEW: Habitual physical activity in patients with myotonic dystrophy type 1: an optimistic sub study

Partner 02 UNEW: Cardiac Magnetic Resonance Imaging: cross-sectional study of 22 Myotonic Dystrophy type-1 patients soon to start an active exercise program.

Partner 02 UNEW: Cardiac Magnetic Resonance Imaging for patients with Myotonic Dystrophy type 1

Partner 02 UNEW: Observational Prolonged Trial In Myotonic dystrophy type 1 to Improve Quality of Life- Standards, a Target Identification Collaboration

Presentations

Partner 01 RUMC: Cognitive behavioural therapy and graded exercise for myotonic dystrophy type 1 (OPTIMISTIC)
 Partner 01 RUMC: Quantitative MRI evaluation of fatty infiltration and edema-like lesions in skeletal muscles of Myotonic Dystrophy type 1.
 Partner 02 UNEW: Studying the hearts of Myotonic Dystrophy type 1 patients with Magnetic Resonance
 Partner 02 UNEW: Myotonic Dystrophy (PhenoDm1)
 Partner 03 LMU: Poster Presentation about the upcoming OPTIMISTIC-Study at the Munich Site
 Partner 03 LMU: OPTIMISTIC-Study at the patient's organisation for myotonic dystrophies
 Partner 04 AHPH: Presentation of the study at five patient representative's regional meetings (2015-2017)
 Partner 05 UGLA: Research in myotonic dystrophy' Patient and family workshops at the Myotonic Dystrophy Support Group Annual Meeting
 Partner 05 UGLA: Myotonic dystrophy: genetics, pathogenesis and drug development' invited presentation at the Muscular Dystrophy UK Myotonic Dystrophy Information Day
 Partner 05 UGLA: Variability in myotonic dystrophy'. Invited presentation for Myotonic Dystrophy Support Group Scottish Meeting
 Partner 05 UGLA: The OPTIMISTIC trial of exercise and cognitive behavioural therapy in myotonic dystrophy' Invited platform presentation to patients and families at the Myotonic Dystrophy Foundation (USA) Annual Conference

Organisation of Conferences / Symposia / Workshops

Partner 01 RUMC and Partner 02 UNEW: 222nd ENMC International Workshop: Myotonic Dystrophy, developing an European consortium - Presentations and talks of all OPTIMISTIC PIs
 Partner 01 RUMC, Partner 02 UNEW, Partner 03 LMU and Partner 04 AHPH: OPTIMISTIC Patient's day
 Partner 05 UGLA: Host, organiser and presenter for Muscular Dystrophy UK Scottish Patient Research Day

Articles / Papers

Partner 01 RUMC: Cognitive behaviour therapy plus aerobic exercise training to increase activity in patients with myotonic dystrophy type 1 (DM1) compared to usual care (OPTIMISTIC): study protocol for randomised controlled trial
 Partner 01 RUMC: Causality on cross-sectional data: Stable specification search in constrained structural equation modeling
 Partner 01 RUMC: Causality on longitudinal data: Stable specification search in constrained structural equation modelling (accepted but not published)
 Partner 02 UNEW: Functional impairment in patients with myotonic dystrophy type 1 can be assessed by an ataxia rating scale (SARA)
 Partner 02 UNEW: The UK Myotonic Dystrophy Patient Registry: facilitating and accelerating clinical research
 Partner 02 UNEW: Risk of falls and fractures in Myotonic Dystrophy: results from a multinational survey (submitted)

Websites/Applications

P8 concentris: Project website: www.optimistic-dm.eu
 P8 concentris, all clinical sites: Information material available for all patients in 4 languages (OPTIMISTIC website)

A detailed publication plan is topic of monthly teleconferences; please see Table 16 (OPTIMISTIC publication plan) for details.

4.3 Exploitation of results of OPTIMISTIC

Within OPTIMISTIC 255 subjects with varying degrees of DM1 severity were recruited into a clinical trial of cognitive behavioural therapy (CBT) and exercise in order to manage their somatic and cognitive symptoms affecting their quality of life. Of these, 30 blood serum samples were selected for RNA sequencing based on their DNA modal repeat length and symptom severity (as assessed by the MIRS rating scale). As outlined in Deliverable 5.1, differential expression of mRNA and miRs are observed that are associated with certain pathways suggesting a key role for specific biological processes. Validating these changes by quantitative polymerase chain reaction (qPCR) and relating them to the clinical phenotype is now under study. Hence ascertaining the strategic utility of this panel is preliminary.

Instead, WP10 chose to focus on a valorisable output. The team of Prof. Heskes (WP8) has developed a causal modelling algorithm which allows the determination of causal relationships and the prediction of which factors most influence a set of variables. The utility of this algorithm either by fee-per-service prediction or the development of a software package for licensing has been explored in the context of a business plan. This plan has recently been outlined and recommends the use of this

algorithm in policy making affecting healthcare and other areas. A more in-depth market analysis is under way and a decision was made to create a company supporting its development.

In addition, the strategic evaluation report/business case for the marketing of DM1 outcome measure markers is not yet complete as the full analysis of potential markers linked to clinical data remains to take place. In WP8 we have developed a causal modelling algorithm which allows the determination of causal relationships and the prediction of which factors most influence a set of variables. The utility of this algorithm either by fee-per-service prediction or the development of a software package for licensing has been explored in the context of a business plan. Since this algorithm has been published and its modifications lie in the public domain, a patent is not possible. However, the know-how regards its implementation is privileged and while not directly patentable, the intention is to create a company supporting its utility in 2017/2018.

5 The address of the project public website, if applicable as well as relevant contact details

www.optimistic-dm.eu