MID Frail

JANUARY 2015

Welcome to the latest issue of the MID-Frail newsletter!

This essential reading provides you with a round-up of news on the latest events in this exciting pan-European study on diabetes in older people.

In this issue…

- Study Status
- New Team Members
- Partner's Contributions

Happy New Year!

Niche wishes every MID-Frail partner a productive and prosperous 2015!

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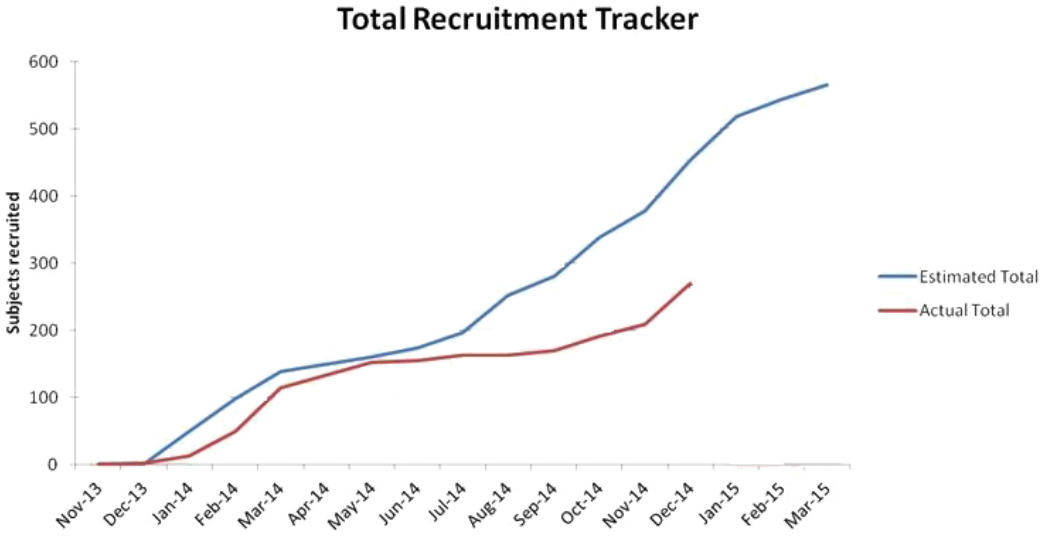
Study Status

Many thanks to Karen Chalk of Niche Science & Technology Ltd. for providing the information on the status of site recruitment at 02 January 2015.

Forty-seven sites are currently active and 275 subjects have been recruited:

- 22 of 24 sites in Spain (eight sites have been randomised)
- 10 of 10 sites in the Czech Republic (five sites have been randomised)
- Five of 10 sites in Bordeaux (one site is randomised)
- Five of 12 sites in Toulouse (two sites have been randomised)
- Two of 12 sites in Germany have been activated (two sites have been randomised)
- Two of seven sites in Belgium have been activated (none have been randomised)
- One of 12 sites in Italy has been activated (this site has not been randomised)

Figure 1 below shows recruitment as expected according to the sites currently active. A recruitment deadline has been set for the end of March 2015.



By Anna Durrance-Bagale – anna.durrance@niche.org.uk
Niche Science and Technology - www.niche.org.uk

New Team Members

Some changes to the MID-Frail team have occurred since our last update. Charlie Cowtan has joined the team at Cardiff University as a research assistant and Anna Durrance-Bagale from Niche Science & Technology has replaced Severina Moreira as the Communications Project Manager.

Charlie Cowtan

'Originally from the Isle of Wight (an island off the south coast of England), I completed my undergraduate Psychology degree in Gloucestershire, and a Master's degree in Abnormal & Clinical Psychology at Swansea University. My main scientific interests focus around mental illness, and the multitude of ways in which people differ from one another, and how people respond differently to the experiences that shape our lives, and in some cases that form the foundations of mental illness. However, if I was to describe myself I would say that I like people. I like helping people, I like working with people and I love studying people. I am interested in the human experience, and the 'fine line' that differentiates mental wellness from mental illness, and where an ordinary human experience becomes a clinical

New Team Members continued...

Charlie Cowtan

'problem'. As such, I have a great deal of interest in depression, anxiety, schizophrenia/psychosis and eating disorders. I am also greatly interested in the ways in which psychological therapies help alleviate emotional distress. Finally, I am also fascinated by the organ itself (the brain) and the changes that are observed neurologically in people who are experiencing dementia as well as on the consequences of stroke and other head traumas, and the ways these changes are managed and rehabilitated in some cases'.

'My involvement with the MID-Frail study as a Research Assistant is first and foremost to assist the statistician in preparing the data for statistical analysis of the main study, and some of the sub-studies. As such, I am working to develop appropriate data-cleaning and statistical analysis plans. I am also working on developing data management plans for our unit, for each of the datasets we are planning to analyse. Though we have no direct involvement in data collection, data entry, data querying or monitoring, I am still required to document in detail how each of these functions have been performed, so that we know precisely where data are coming from and what procedures were followed to guarantee the integrity of the data we are analysing'.

Charlie can be contacted on CowtanC@cardiff.ac.uk.

Anna Durrance-Bagale

Anna, House Editor at Niche Science and Technology, has been with the company for 10 years. A highly experienced regulatory writer and editor with a background in neuroscience, Anna has written and/or edited hundreds of regulatory and other types of documents over the years for many pharmaceutical companies. Anna is also responsible for mentoring new members of staff at Niche, and runs writing and editing workshops for clients. In her spare time Anna runs a small fairtrade craft business and is an enthusiastic traveller, visiting places as far flung as Nepal, Iran and Kyrgyzstan.

Please let Anna know every time you prepare an abstract, poster or oral presentation for a conference. As Niche is serving as a repository for all publications you can also contact Anna to obtain information on what the other partners have presented or are planning to present.

Anna is happy to be contacted by email at anna.durrance@niche.org.uk
or by phone on +44 (0)20 8332 2588.

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Partner Contributions

We were delighted to receive two partner contributions for this edition of the MID-Frail newsletter. This is an excellent way of sharing interesting and relevant study information and we want to thank both Karen and Sophie for their contributions. Please do get in touch with Anna if you would like to prepare something for inclusion in the next newsletter.

Rotterdam Meeting 17 September 2014

By Karen Chalk, on behalf of Niche Science & Technology

A successful meeting was held on 17 September in Rotterdam between the MID-Frail partners. The meeting served as a useful opportunity to introduce new members of the team, be updated on progress in the study and to discuss the next steps in this exciting project. The main outcome of the meeting was the importance of improving recruitment over the next few months; the deadline for completing recruitment is 31 March 2015.

The meeting was held at the NH Atlanta and was ably organised by Olga Laosa Zafra. Professor Leocardio Rodríguez-Mañas opened the meeting with a summary of the challenges faced to date and a review of the future of the project. It was acknowledged that there had been several delays to the study (mainly of an administrative nature) but that most of these had now been overcome. The importance of completing recruitment by 31 March 2015 was highlighted and all partners were asked to make every effort to ensure that all their sites are recruiting as soon as possible. It was reported how a meeting was held with a representative from the EU in October to discuss the study progress and, although the EU are aware of the delays to date, the EU representatives had emphasised how further delays should be avoided.

The safety profile of the study to date was reviewed and it was noted that although the profile of the study population means that we might expect a lot of SAEs, most of these are likely to be related to co-morbidities rather than a consequence of the study procedures. However, it is also important that every effort should be made to report SAEs according to the protocol, whether they are related to the study or not.

Karen Chalk gave a presentation outlining the current study status in the different countries, an overview of which is summarised in Figure 2.

Specific details of progress were discussed for each country. The most frequently cited reasons for delays in sites starting recruitment are related to issues around obtaining ethics approval and contract finalisation. A positive piece of news announced during the meeting was that Genefrail had been approved in France.

A short presentation was then given by or on behalf of each country:

Czech Republic (Professor Eva Topinkova): all sites are now actively recruiting in the Czech Republic. There have been several updates

Country	Centres active/ planned	Percentage centres active	CE Granted	Subjects recruited /planned	Percentage subjects recruited
Belgium	0/11	0%	Add Information required and submitted for Central EC	0/165	0%
Bordeaux	5/12	42%	ALL (Mid Frail) Pending for Genefrail	6/180	3%
Czech Republic	6/11	55%	All	64/165	39%
England	0/11	0%	Central EC approval granted. Pending R&D	0/165	0%
Germany	0/12	0%	10	0/168	0%
Italy	0/12	0%	3 approvals for MID Frail 2 approvals for Genefrail	0/180	0%
Spain	14/23	61%	22	97/333	29%
Toulouse	1/12	8%	ALL (Mid Frail) Pending for Genefrail	0/180	0%
Wales	0/12	0%	Central EC approval granted. No list of TS provided	0/168	0%

to the ethics committee due to the original submission occurring early on. The major issue the team have had is patient recruitment, as most sources of referral send only a few potential subjects.

Bordeaux (Karen Chalk): five sites have been activated and four are pending agreement on the contracts. Nineteen subjects have completed Sensole Part 1 and this sub-study is on track to complete recruitment (30 subjects) shortly.

Toulouse (Karen Chalk): one site is active but recruitment has not yet begun. Other sites are pending an amendment to the European Commission that occurred in October.

Wales (Professor Antony Bayer): ethics approval has been granted but there are difficulties identifying sites in Wales due to cost implications. It was noted that sites could be recruited in England but paid out of the Welsh budget and this approach will be pursued by Professor Bayer and Professor Sinclair.

England (Professor Alan Sinclair): central ethics approval has been granted and R&D submissions are in progress. Seventeen sites have currently shown interest. Sites will mainly be based at general practitioner (primary care physician) practices rather than in hospitals.

Spain (Olga Laosa Zafra): ethics approval has been granted at 22 sites of which 14 are recruiting. Eight of these 14 sites are randomised. Recruitment is on track to complete within the timelines specified.

Belgium (Stefanie Buyser): there were originally 11 sites but some have dropped out for various reasons leaving seven sites currently involved. Work is ongoing to try and identify additional sites but this is difficult. The ethics submission is currently being reviewed and a response from the committee is expected shortly.

Italy (G. Paolisso): two of the original 12 sites have withdrawn and replacements are being sought. Almost all sites have been initiated and start-up documents are being collected. The main delay is due to issues obtaining local ethics approval. Potential subjects can be identified easily from patient lists but it is not known if they will participate.

Germany (Karen Chalk): no sites are currently recruiting. Initiation has occurred at several sites and start-up documents are being collected.

By Anna Durrance-Bagale – anna.durrance@niche.org.uk
Niche Science and Technology - www.niche.org.uk

Other points discussed included:

- Timing of partner meetings: it was generally agreed by those present that co-locating them with conferences was a good way forward.

- Frail or pre-frail patients: it was noted that in some countries most subjects are pre-frail. The general feeling was that this would not be an issue due to the downward trajectory of the health of these patients. More research will be performed into the distribution of the subjects already recruited.

- Exercise intervention: subjects should complete at least 80% of the exercise sessions to be classed as compliant. Breaks in the exercise regimen should ideally be no more than 1-2 weeks.

Mark Kelson gave a presentation on the statistical aspects of the study. Depending on rates of recruitment there is between a 20 and 58% power that we will show a difference if recruitment finishes in March. Sites have been asked not to recruit more than 18 subjects. Increasing site size would potentially allow for more subjects to be recruited but the cluster randomisation method would reduce the power for that number of subjects. From a statistical point of view using more sites with a smaller number of subjects is a better option if possible. Ideally sites will be a similar size.

Ignacio Jiminez gave a presentation on the Genefrail sub-study and presented results from the eight subjects who have undergone analysis so far. Operational procedures for sample shipment were reviewed – please contact Olga or Karen when samples are ready for shipment.

Luz Maria Pena introduced the protocol relating to the economic cost analysis for the study. The requirements for data at both a country and a site level were reviewed and the timelines identified. Site data will only be required from one site and MID-Frail partners have been asked to identify the site for their country by 01 November 2014.

The meeting was closed by Professor Rodríguez-Mañas and Professor Sinclair who expressed optimism about the future progress of the study while acknowledging the efforts that we all need to make to encourage continuing recruitment.

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Partner Contributions continued...

Sensole Sub-Study Part I

By Professor Isabelle Bourdel-Marchasson (co-ordinator for the CHU of Bordeaux, France sites and Work Package 6 leader), Joël Poustis (leader of Sensole sub-study), and Dr Sophie Regueme (research engineer/bioexpert for Sensole sub-study)

The most frequently reported long-term complication of diabetes is diabetic sensorimotor polyneuropathy, which leads to progressive fibre degeneration and perception sensory loss via increased sensory thresholds of mechanoreceptors and changes in the characteristics of the afferent fibres.[1,2]

The ability to maintain balance during standing partly results from shear stresses and changes in pressure that are mediated by the plantar mechanoreceptors. Consequently, the loss of somatosensory information from the cutaneous mechanoreceptors of the foot in elderly and/or diabetic patients leads to postural instability,[3–7] increased risk of falling, and dependency. Based on previous studies demonstrating that a superposition of a mechanical noise could enhance afferent sensory input[5,8,9] and improve balance control[6,7,10] in elderly patients with diabetes, Joël Poustis, Director of Hexabio R&D, SARL has developed an innovative insole device (French Patent N° 09 04955 - October 2009 and N°11 03355 - 2011).

Vibrating motors are inserted into each insole under both the anterior and posterior parts of the plantar foot surface. The innovative Hexabio R&D insole concept relies

Interesting MID-Frail fact

Although it has not yet been cited in the scientific literature the MID-Frail protocol manuscript has been viewed 122 times and downloaded 79 times.

on the membrane that enables a propagation of the vibration on the whole insole, allowing ageing- and/or diabetes-induced changes in the distribution of foot pressure. To our knowledge, potential effects on everyday balance (e.g., walking) caused by postural sway associated with vibrating insoles have not been studied. As daily hospital visits are inconvenient for patients, a plantar mechanoreceptor stimulation device that frail, diabetic patients can use at home has great potential.

The Sensole sub-study is designed to investigate the effects of the Hexabio R&D insole concept on gait and posture among older patients with diabetes, examining impact on everyday balance and quality of life (Sensole Part I). To date, 26 older patients (85 ± 6 years, range 74–101 years, 14 men and 12 women; 30 patients are anticipated) with diabetes have been enrolled in Sensole Part I. Potentially eligible patients are screened for their autonomy in daily living tasks (Barthel index $\geq$60), the presence of ulcerations and/or infections on the plantar surface of the feet, and the presence of a pace-maker: if patients have either of the last two they are ineligible. The study is being conducted according to the Declaration of Helsinki (2008) and approved by the Local Committee for Human Protection in Biomedical Research (n°2013/78). All patients provided written informed consent.

Gait and posture are assessed through: the Short Physical Performance Battery (balance test /4; 4 m walking

test /4; repeated chair stand test /4); the Time Up and Go test (stand up, walk 3 m at regular pace, turn around, walk back, and sit down); and the frequently used posturographic standing test (30 seconds eyes closed, Figure 3), providing among others the displacements and surface area of the centre of pressure (mm²). These tests are done just before and after a 20-minute vibration session and are repeated a further 15 minutes. The sensitivity of the plantar foot is assessed using a monofilament (under the first and fifth metatarsal and the heel) and the vibration threshold perception (smallest vibration frequency perceived by the patient) just before the vibration session. During the latter, patients are seated with their feet on the insoles for 20 minutes (Figure 4). The vibration frequency is set at 90% of the pre-determined vibration threshold.

Figure 3: Posturographic measurements on the double force platform.

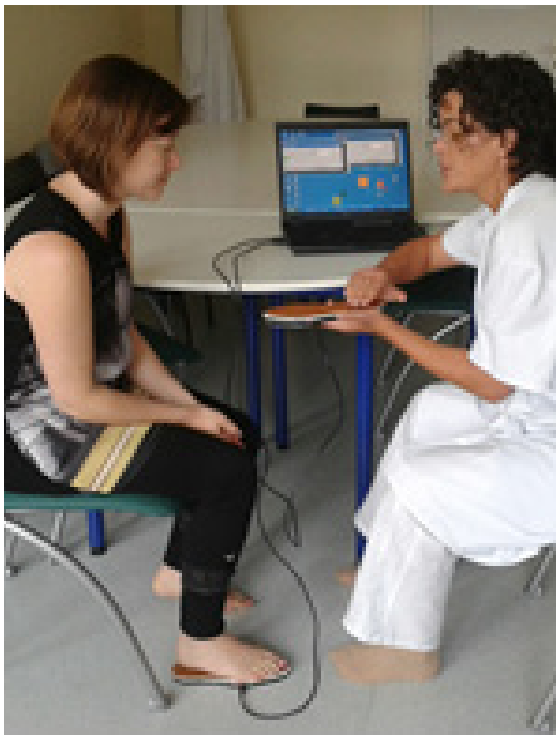

Figure 4: Explaining the insole device.

The data produced from the first part of the Sensole sub-study will be used to submit to the regulatory authorities before Part II (i.e., the 1-month home intervention).

By Anna Durrance-Bagale – anna.durrance@niche.org.uk
Niche Science and Technology - www.niche.org.uk

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KEEP UP TO DATE

Keep up to date on all that is happening in MID-Frail: watch out for the next regular issue of MID-Frail News.

Website: **www.midfrail-study.org** Facebook: **MID-Frail Clinical Study**