



Feb
2016

now includes updates on
the MID-Frail project



In this issue...

- Frailomic Meetings
Geneva, Switzerland,
15– 16th October
2015
Mallorca, 12–13th
November 2015
- Publications update
- MID-Frail news
- Conferences

This newsletter contains news from Frailomic and combines recent updates on the MID-Frail project.

Following a challenging start, the subject recruitment phase of the MID-Frail study has finally closed. As the MID-frail recruitment period was extended the project no longer has sufficient resources for their newsletters to continue. It was agreed by the Frailomic project lead, Professor Leocadio Rodriguez-Man  s that combining important updates in a joint newsletter would be a great way to continue sharing information among the teams.

In this edition we report on the Frailomic meetings held last year in Geneva, Switzerland on the 15th–16th October 2015 and in Mallorca on the 12th–13th November 2015. These meetings mark an important milestone for the beginning of the project’s second phase. Now that the MID-Frail study has reached the end of subject recruitment, we can now share the total subject numbers. We also include a list of upcoming conferences as a new resource which partners may find useful in planning future presentations.

Please read on to enjoy hearing about the recent events and further news from our individual partner organisations.

DO NOT SHARE

Please remember NOT to share the contents of this particular issue of newsletter as it contains confidential information that should only be available to Frailomic and MID-Frail partners (please note that it will not be made available on the consortium websites).

End of Exploratory Phase Meeting

15th–16th October 2015 – Geneva, Switzerland

By Laila Guzadhur, on behalf of Niche Science & Technology
(with thanks to Mónica Ballesteros for sharing the minutes taken during the meeting)

As Phase 2 of our journey begins, the analysis of the data from Phase 1 reveals some significant relationships between biomarkers and the development of frailty. The objective of the meeting in Geneva was to update the attendees on the initial results from the statistical analysis, ahead of the November 2015 Frailomic consortium meeting in Mallorca. Assistant Professor David Gómez-Cabrero presented the results from the data analysis over the course of two days.

Harmonisation

David started his presentation by describing some of the problems during the data harmonisation stage. Some issues arose due to ambiguities in the classification of the types of alcohol consumed. Where data was missing this may have denoted 'no consumption'. Information on chronic diseases will also need updating and will require clarification through follow up data.

Analysis

The analysis was structured according to the three Frailomic objectives. Data were tested to identify biomarkers which could be involved in (i) diagnosing frailty, (ii) predicting frailty and (iii) the prognostic outlook for frailty. Five questions were designed and the biomarkers were tested for significant associations with each question:

- Which biomarkers are involved in the separation between robust, pre-frail and frail?
(all individuals)
- Which biomarkers are involved in the separation between robust, pre-frail and frail?
(in non-disabled individuals)
- Which biomarkers are associated with a risk of becoming frail?
(in robust and pre-frail, pre-frail and frail, excluding "pre-frail to robust" trajectory)

- Which biomarkers can be used as predictors for death?
(in frail and pre-frail individuals)
- Which biomarkers can be used as predictors for disability?
(in non-disabled individuals)

Results

David explained how the candidate biomarkers involved in the development of frailty were selected. Biomarkers with a permuted p-value and a computed false discovery rate below defined thresholds (depending on the biomarker category) were considered to demonstrate a significant association with any of the five questions when tested. A meta-analysis across cohorts was also included where possible. Biomarkers showing significant results were mostly observed with the

first two questions, which involved the diagnosis of frailty. This is due to the current study population having a small, under represented proportion of disabled individuals and observed deaths.

Meeting Conclusion

At the end of the Geneva meeting, it was decided that the main results would be compiled and distributed to the partners of the project. This is now available as the statistics report for the first phase of the Frailomic Initiative, which was prepared for the Mallorca meeting. If you haven't received this, or need a copy, then Niche can send this to you. The next steps for biomarker modelling, involves the generation of minimal predictive models, which David discussed in more detail in Mallorca. Read on to find out more!

Meeting Participants

The six members of the Frailomic team who met in Geneva, Switzerland were David Gomez-Cabrero (You Health), Somnath Chatterji, Emese Verdes (World Health Organization), José Antonio Carnicero Carreño, Mónica Ballesteros and Leocadio Rodríguez-Mañas (Fundación para la Investigación Biomédica – Hospital Universitario de Getafe).

“Next steps” (Mallorca)

At the Mallorca meeting in November, there was a large turnout of about 40 members of the Frailomic team! Professor Leocadio Rodriguez-Manás gave a warm welcome and emphasized the importance of following the publications process. The consortium also need to take into account some of the problems in the first phase to avoid future inconveniences in the second phase.

Some of the problems encountered by the partners during the first phase of the study were conveyed by Monica and prompted useful discussions to help the consortium realise their expectations of the Frailomic project in 2016.

This was followed by David’s spectacular presentation of the analysis to all the Frailomic partners who attended the

meeting. He also presented further findings in generating the minimal models. The aim of the minimal models is to find an optimal point at which the combination of features is minimal, but provides a maximal predictive power. Generation of minimal models involved two steps. The first step of



Mónica Ballesteros introduced the results obtained from the second year of the Frailomic project. Thank you to all the partners who completed the pre-meeting questionnaire and provided feedback.

feature selection was the pre-selection of variables (i.e., candidate variables) to be considered for the predictive models. In the second step, biomarkers were selected from a series of over 250 imputations

per cohort for their predictive power. Those found to have high rankings were selected as variables for the predictive minimal models. The outcome was a list of variables to be included in the minimal models. David also described the associations between variables according to cohort.

The feature signatures of biomarkers have now been identified and selected. The minimal models, in the form of a list of selected biomarkers, have been distributed to the partners. It was also discussed at the meeting that further work could include stratification of subjects by age. It was agreed that representatives from the Cohorts would also discuss their thoughts with David. This could provide further insights from all perspectives into some encountered issues, or perhaps factors to take into consideration. A huge thank you to David for his skills in accomplishing such a feat!

Thanks must also go to Francisco Mansoa for an update on the Frailomic budget and for explaining the new process for managing and submitting the annual financial reporting process. Attendees of

the Mallorca meeting were also provided with a comprehensive background on intellectual property, patenting and commercialization of products that may arise from the Frailomic initiative. Thank you Mario Romero Torre, from Idetra, for re-iterating the publication policy and for explaining the technology identification methodology (TIME) model used in technology transfer.



All the presentations given at the Mallorca meeting have been emailed to the Frailomic partners. If you haven't received these, please let us know and we can send you the copies.

Sample Distribution and Data Sharing

Monica reminded the partners of the BSCW file sharing platform and invited partners to use it as a helpful resource. The procedure for sending and receiving samples from the cohorts to the laboratories was also described and a spreadsheet was sent to all partners in December 2015 for the start of Phase 2.

We are now in the fortunate position to have data on the biomarkers investigated in Phase 1. Several partners kindly declared

they would like to share the data from their respective laboratories within the Frailomic consortium. Partners will need to give their consent to the sharing of data and are requested to complete a consent document. The form has been circulated to all partners and can be obtained from Niche and the Frailomic project manager.

We wish everyone the very best for Phase 2 of the Frailomic Initiative!



Partner News

New Project Manager

It was with great sadness that we must announce that Mónica Ballesteros has left the role of Frailomic project manager from the middle of January 2016. We are very sorry to be saying goodbye to Monica, however she has done a great job and we wish her all the best with her PhD in Public Health at the Universitat Autònoma de Barcelona.

welcome and thank you to Betty as she joins our team while the project enters its most exciting phase so far!

Congratulations to Edoardo Fiorillo for his recent television interview on his work at the Institute for Genetic and Biomedical Research, Italian Research Council. He was interviewed as one of the key scientists



Television interview of Edoardo Fiorillo

Dr. Betty Davies Urizar is now the project manager for the Frailomic initiative. We hope you will join us in giving a warm

researching the genetic traits involved in Sardinia's population and longevity in the Sardinian research program.

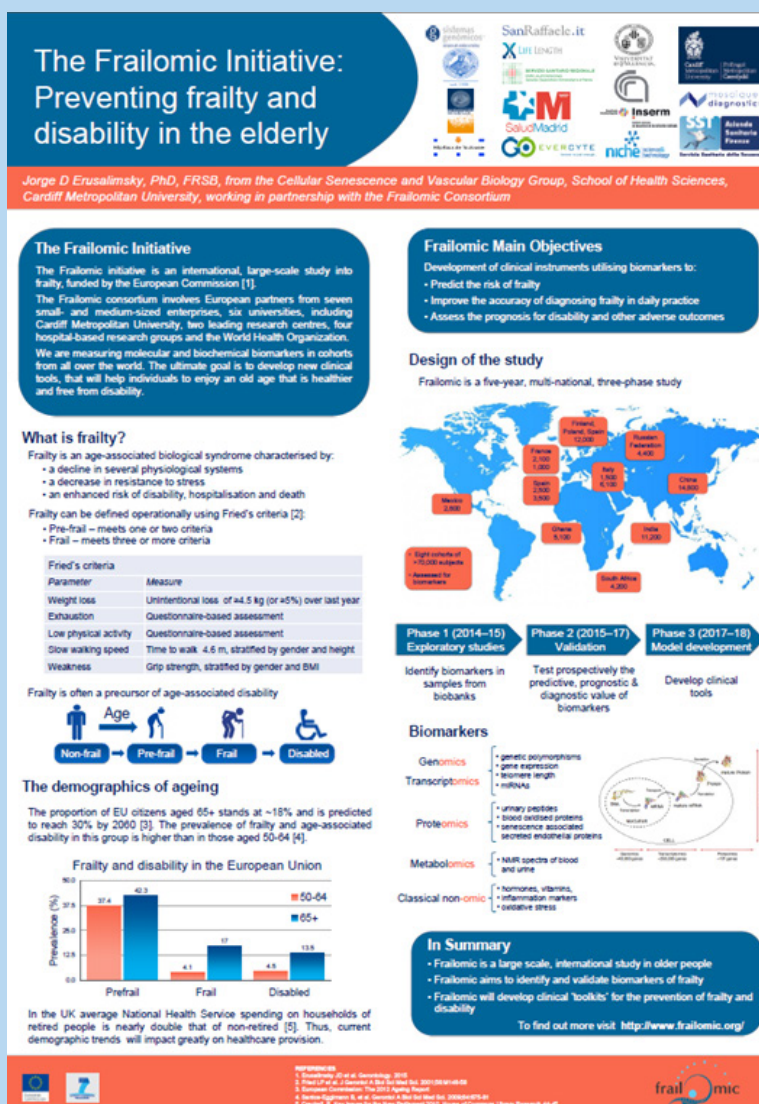
Publications Update

The Frailomic Consortium has been actively producing manuscripts, posters and abstracts to publicise the work being undertaken by the initiative.

- The manuscript: 'In Search of 'Omics'-Based Biomarkers to Predict Risk of

Frailty and Its Consequences in Older Individuals: The Frailomic Initiative' was published online in July 2015. Copies of the manuscript are now available at the journal website. The manuscript was also accompanied by a methodology poster presented by Professor Erusalimsky and Dr Lee Butcher from Cardiff Metropolitan University, at a public health research event held in November in Cardiff. The event was attended by approximately 100 delegates. The aims of the event were to raise awareness of the research activities taking place across Wales and to strengthen collaborations between research institutions, the public sector and the public to facilitate an informed contribution towards future policies and programmes. Thank you to Professor Erusalimsky for securing an invitation from the Editor-in-Chief and for co-ordinating the poster presentation of the Frailomic Initiative in Cardiff.

- The Letter to the Editor 'Laboratory biomarkers and frailty: presentation of the Frailomic Initiative' was published



The Frailomic Initiative: Preventing frailty and disability in the elderly

Jorge D Erusalimsky, PhD, FRSB, from the Cellular Senescence and Vascular Biology Group, School of Health Sciences, Cardiff Metropolitan University, working in partnership with the Frailomic Consortium

The Frailomic Initiative
The Frailomic initiative is an international, large-scale study into frailty, funded by the European Commission [1]. The Frailomic consortium involves European partners from seven small- and medium-sized enterprises, six universities, including Cardiff Metropolitan University, two leading research centres, four hospital-based research groups and the World Health Organization. We are measuring molecular and biochemical biomarkers in cohorts from all over the world. The ultimate goal is to develop new clinical tools, that will help individuals to enjoy an old age that is healthier and free from disability.

Frailomic Main Objectives
Development of clinical instruments utilising biomarkers to:
• Predict the risk of frailty
• Improve the accuracy of diagnosing frailty in daily practice
• Assess the prognosis for disability and other adverse outcomes

Design of the study
Frailomic is a five-year, multi-national, three-phase study

What is frailty?
Frailty is an age-associated biological syndrome characterised by:
• a decline in several physiological systems
• a decrease in resistance to stress
• an enhanced risk of disability, hospitalisation and death
Frailty can be defined operationally using Fried's criteria [2]:
• Pre-frail – meets one or two criteria
• Frail – meets three or more criteria

Fried's criteria	Parameter	Measure
Weight loss	Unintentional loss of ≥4.5 kg (or ≥5%) over last year	
Exhaustion	Questionnaire-based assessment	
Low physical activity	Questionnaire-based assessment	
Slow walking speed	Time to walk 4.6 m, stratified by gender and height	
Weakness	Grip strength, stratified by gender and BMI	

Frailty is often a precursor of age-associated disability

The demographics of ageing
The proportion of EU citizens aged 65+ stands at ~18% and is predicted to reach 30% by 2050 [3]. The prevalence of frailty and age-associated disability in this group is higher than in those aged 50-64 [4].

Frailty and disability in the European Union

Category	50-64	65+
Pre-frail	37.4	40.3
Frail	4.1	17
Disabled	4.5	13.6

In the UK average National Health Service spending on households of retired people is nearly double that of non-retired [5]. Thus, current demographic trends will impact greatly on healthcare provision.

Phases of the study
Phase 1 (2014-15) Exploratory studies: Identify biomarkers in samples from biobanks
Phase 2 (2015-17) Validation: Test prospectively the predictive, prognostic & diagnostic value of biomarkers
Phase 3 (2017-18) Model development: Develop clinical tools

Biomarkers
Genomics: genetic polymorphisms, gene expression, telomere length, miRNA
Transcriptomics: urinary peptides, blood oxidized proteins, senescence associated secreted endothelial proteins
Proteomics: NMR spectra of blood and urine
Metabolomics: hormones, vitamins, inflammatory markers, oxidative stress
Classical non-omic

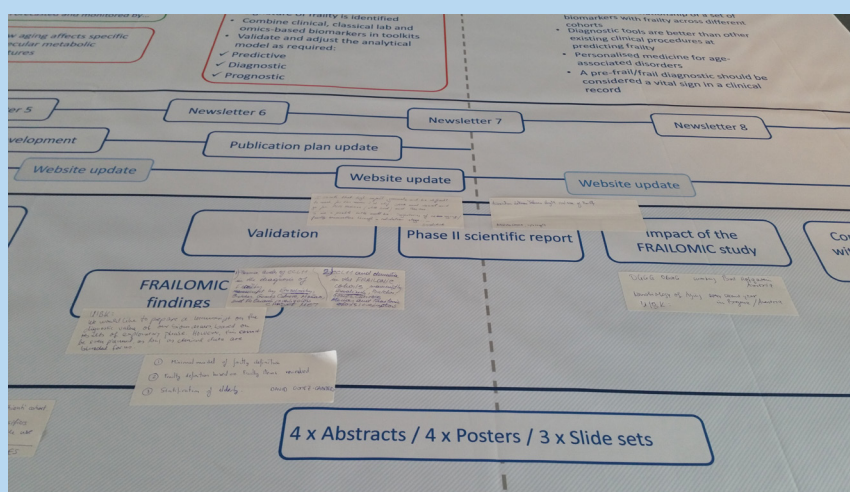
In Summary
• Frailomic is a large scale, international study in older people
• Frailomic aims to identify and validate biomarkers of frailty
• Frailomic will develop clinical 'lookits' for the prevention of frailty and disability
To find out more visit: <http://www.frailomic.org/>

online in the journal 'Clinical Chemistry and Laboratory Medicine' in March 2015. Well done to the authors of the letter on behalf of the Frailomic Consortium. The letter was authored by Giuseppe Lippi, Pidder Jansen-Duerr, Jose Viña, Anna Durrance-Bagale, Imad Abugessaisa, David Gomez-Cabrero, Jesper Tegnér, Johannes Grillari, Jorge Erusalimsky, Alan Sinclair and Leocadio Rodriguez-Manñs.

- Catherine Feart presented two Frailomic related abstracts at the International Academy of Nutrition and Ageing (IANA) conference, which was held in Barcelona, Spain, earlier this year, in June 2015. The IANA has an overarching theme of preventing frailty and the meeting covered a range of topics, including cellular responses to nutritional research in populations. Details of the next IANA meeting and other conferences, that you may like to present at or submit a poster to, are listed at the end of this Newsletter.
- Niche Science & Technology have been working with Dr Jose Viña to develop a manuscript entitled 'mRNA analysis in centenarians reveals specific patterns associated with control of apoptosis and cellular senescence'. After an initial submission to Nature Communications the editor granted a chance for resubmission if some experiments were undertaken. However, upon

additional experiments and revision, the manuscript was rejected after peer-review. The authors are now considering which journal to target next.

- The second review is an epidemiology-based review of frailty and is currently being developed by the authors.



During the meeting in Mallorca, partners were invited to express their interest in publishing manuscripts, abstracts, or poster communications during Phase 2 of the Frailomic project. Thank you to those partners who volunteered their interest to publish manuscripts. Through the poster based activity we were able to gain insights across the consortium for the future direction of publications (even if the poster refused to co-operate and kept falling to the floor!). The upside is that we are looking forward to having more publications from the Frailomic community!

Study Status

We have reached a major milestone for the MID-Frail project. MID-Frail now has a total of 928 recruited subjects. The numbers of subjects per country are now:

- 270 subjects have been recruited from across 20 sites in Spain (25 sites in total)
- 94 subjects from seven sites in the Czech Republic (ten sites in total)
- 85 subjects from nine sites in Bordeaux (ten sites in total)
- 143 subjects from nine sites in Toulouse (twelve sites in total)
- 81 subjects from five sites in Germany (ten sites in total)
- 37 subjects from five sites in Belgium (seven sites in total)
- 101 subjects from nine sites in Italy (12 sites in total)
- 117 subjects from 14 sites in the UK (20 sites in total)

Well done to all the sites and to those individuals whose collective effort led to such a successful recruitment. Figure 1 below shows the level of recruitment over the last two years.

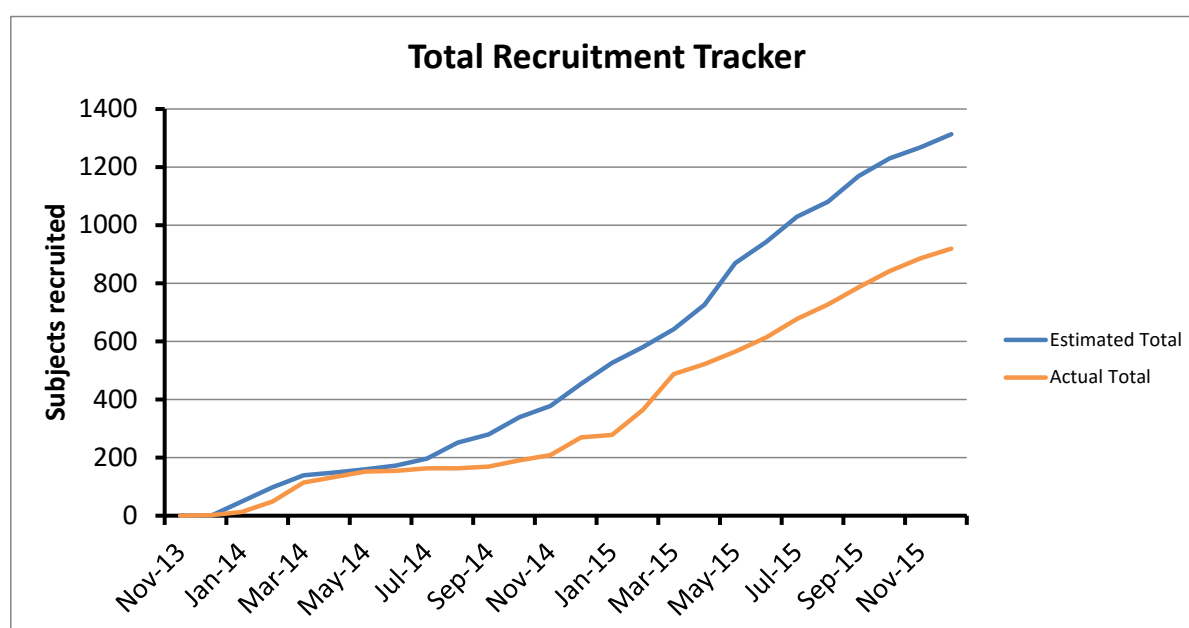


Figure 1: MID-Frail subject recruitment

Introduction of the MID-Frail Intellectual Property Committee

The IPC for MID-Frail has now been confirmed and there is a publications process in place for all MID-Frail related publications. Members of the MID-Frail IPC, responsible for overseeing the publications are:

- Alan J Sinclair (Project Scientific Co-ordinator), representing Diabetes Frail Ltd. Chair of the IPC.
- Andrej Zeyfang representing the University of Ulm, Ulm, Germany
- Mikel Izquierdo representing the Public University of Navarra, Spain
- Isabelle Bourdel-Marchasson representing the CHU of Bordeaux, Bordeaux, France
- Giuseppe Paolisso representing the University of Naples, Italy
- Luz Maria Peña-Longobardo representing University of Castilla-La Mancha, Spain
- Eva Topinkova representing Charles University, Czech Republic
- Giovanni Gambassi representing Università Cattolica del Sacro Cuore, Italy
- Tim Hardman representing Niche Science & Technology, United Kingdom
- Leocadio Rodríguez Mañas (project co-ordinator), representing Hospital Universitario de Getafe, Spain

Niche have circulated the publications process document, however if you require a copy we are more than happy to send them out.

Publications Update

A poster for the Sensole, part 1 study: "Evaluation of a therapeutic insole device on postural stability in older people with Type 2 diabetes" was presented by Sophie Regueme at the International Academy on Nutrition and Ageing (IANA) 2015 meeting. The themes of the meeting were prevention of frailty and loss of function with advancing age. All proceedings from the meeting are published in the Journal of Nutrition, Health and Ageing (JNHA). Sophie has also submitted the corresponding manuscript to Gait and Posture – so we have our fingers crossed for a favourable outcome!

The MID-Frail project was also highlighted at the Public Health Wales Showcase Event in November 2015. Dr Shantini Paranjothy of Cardiff University was a speaker at the event and she described current work being undertaken at Cardiff to further understand the biological and behavioural aspects of health in children and adults. MID-Frail featured as part of Dr Paranjothy's presentation with regard to the development and evaluation of clinical tests and intervention strategies to reduce the impact of ageing on individuals and society.

EVALUATION OF A THERAPEUTIC INSOLE DEVICE ON POSTURAL STABILITY IN OLDER PEOPLE WITH TYPE 2 DIABETES (SENSOLE feasibility study)

Sophie C. Regueme¹, Alexandra Delmas², Hamid Laksir³, Charles Cowtan³, Mark Kelson³, Joël Poustis², Isabelle Bourdel-Marchasson^{1,4}, on behalf of the MID-Frail Consortium

(1) Gerontology department, University Hospital (CHU) of Bordeaux, Bordeaux, France; (2) Hexabio, R&D (SARL), Pessac, France; (3) South East Wales Trials Unit, School of Medicine, Cardiff University, Cardiff, United Kingdom; (4) University Bordeaux and CHRS, BMSB, UMR 5536, Bordeaux, France

PURPOSE
Diabetes is known to be associated with increased frailty, functional decline, and injurious falls. It has been shown that a superposition of a mechanical noise (stochastic resonance mechanism) can enhance afferent sensory input and improve touch sensitivity in patients with diabetic neuropathy, resulting in a better balance control in diabetic older patients. It is therefore of great interest in the context of diabetes and frailty to explore a self-administered intervention of plantar mechanoreceptor stimulation, using a specially designed vibrating insole device (HEXABIO R&D, sarl), on gait and posture in older people with type 2 diabetes (T2D).

METHODS
Non-randomised pilot study assessing the safety of the Hexabio vibrating insoles immediately before and after, and 15 minutes after, a 20-min vibrating sequence. Thirty T2D patients (15 men, 15 women) of the University Hospital of Bordeaux (France) aged 70 years and older participated in the study. Exclusion criteria were: Barthel score <60; inability to carry out the Short Physical Performance Battery (SPPB) test; plantar ulcers and/or infections on the plantar surface of the feet; pace-maker, inability to give informed consent.

Primary objective
Assess the potential insole-induced changes in the Centre of Pressure (CoP) sway area, while standing in eyes closed condition, immediately after, and 15 minutes after, the vibrating sequence.

Secondary objectives
- Measure the presence of neuropathy (monofilament).
- Assess the potential insole-induced changes in SPPB, in Timed Up and Go (TUG) tests and in medio-lateral and antero-posterior CoP displacements.

Statistical analyses
Complete case ANCOVA were used for the CoP sway area change with follow-up CoP scores predicted using baseline CoP, gender, age, and baseline SPPB and TUG tests. According to a Delphi questionnaire answered by eight physiotherapists and physical medicine practitioners, a 40% increase in CoP sway area from baseline (with eyes open) in more than one patient could be considered a significant negative change.

RESULTS & DISCUSSION

Primary outcome: Controlling for baseline CoP sway area, SPPB, TUG, gender and age, the sway area was reduced by 30% at immediate follow-up (coefficient: 0.7, 95% CI: [0.52, 0.87]) and by 53% at 15-min follow-up (coefficient: 0.47, 95% CI: [0.25, 0.70]). Sensitivity analyses of a log transformed sway area indicated a similar reduction at immediate follow-up (logged coefficient: 0.84, 95% CI: 0.63, 1.05) and 15 minute follow-up (logged coefficient: 0.70, 95% CI: 0.37, 1.03) albeit not statistically significant.

Secondary outcomes: no statistically significant changes in SPPB or TUG at either immediate or 15 minute follow-ups.

Baseline characteristics

Age	70.8 ± 5.2
Weight (kg) (mean ± s.d.)	85.8 ± 15.7
Neuropathy (N %)	8 (27%)
Vibration threshold (Hz) (mean ± s.d.)	102.8 ± 57.4
Balance test (s)	2.7 ± 1.9
Walking test (s)	1.9 ± 1.5
Chair test (s)	1.0 ± 1.2
Total TUG	5.6 ± 3.4
TUG (N) (mean ± s.d.)	25.2 ± 20.3
Normal (TUG) (N %)	2 (7%)
Classified mobility (10-15) (N %)	14 (47%)
Problems (CoP) (N %)	11 (35%)

SPPB: Short Physical Performance Battery
TUG: Timed Up and Go

Table 1: CoP changes (baseline to immediate follow-up)

CoP sway area (cm²)	Baseline	Immediate follow-up	15 min follow-up	Number of patients with increase
Normal (TUG)	490.2 ± 100.4	440.0 ± 100.0	400.0 ± 100.0	0
Classified mobility (10-15)	490.2 ± 100.4	340.0 ± 100.0	300.0 ± 100.0	0
Problems (CoP)	490.2 ± 100.4	340.0 ± 100.0	300.0 ± 100.0	0

Table 2: CoP changes (baseline to 15 min follow-up)

CoP sway area (cm²)	Baseline	15 min follow-up	Number of patients with increase
Normal (TUG)	490.2 ± 100.4	300.0 ± 100.0	0
Classified mobility (10-15)	490.2 ± 100.4	250.0 ± 100.0	0
Problems (CoP)	490.2 ± 100.4	200.0 ± 100.0	0

ACKNOWLEDGMENT
SPONSOR: Fundación para la Investigación Biomédica del Hospital Universitario de Getafe. Financial support: Research and Innovation Health European Program FP7: NCT01654341.
FUNDING: European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°278803, MID-Frail Project.

Future publications and conferences

Listed below are some conferences that may be of interest to partners of the Frailomic and MID-Frail consortia. Some deadlines for abstract submission may have passed, but the details are provided here for those who would like to attend.

If you have a manuscript, letter to the editor, abstract, or any other type of document that you'd like to prepare, don't forget to lodge your intentions to publish to the intellectual property committee via Laila at Niche Science and Technology and remember that Niche is always here to help in any way we can.

- WCO-IOF-ESCEO: World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Disease
14–17th April, Malaga (Spain). Deadline for abstract submission passed.
<http://www.wco-iof-esceo.org>
- International Conference on Frailty and Sarcopenia Research (ICFSR)
28—29th April, 2016, Philadelphia, USA. Late call for abstracts 3— 23rd February 2016.
- Epigenetic and Metabolic Regulation of Aging and Aging-Related Diseases.
1–5th May 2016 New Mexico, USA. Deadline for abstract submission passed.
- International Symposium on Neurobiology and Neuroendocrinology of Aging:
17–22nd July 2016, Bregenz, Austria. Deadline for abstract submission 15th May 2016.
<http://www.neurobiology-and-neuroendocrinology-of-aging.org>

continued...

- IANA (International Academy on Nutrition and Ageing):
7–8th July 2016 at Hotel Albuquerque, Old Town Albuquerque, New Mexico, USA.
Deadline for abstract submission passed.
<http://som.unm.edu/cme/2016/pdf/2016-iana-flyer.pdf>
- European and Word Congresses of Geriatric Medicine and Gerontology (EUGMS)
5—7th October 2016, Lisbon, Portugal.
Deadline for abstract submission 15th May 2016
<http://www.eugms.org/2016.html>
- Society for Free Radical Research Europe 8–11th June 2016: Budapest (Hungary),
at the Danubius Thermal Hotel Helia.
Deadline for abstract submission 14th March 2016
<http://sfrr-e-2016.hu>
- International Association of Gerontology and Geriatrics (IAGG) World Congress
July 2017, San Francisco, California
- 21st International Congress of Nutrition
22—27th Oct 2017, Buenos Aires, Argentina

If you have any news that you would like to share with all in the next newsletter, please do get in touch – we'd be delighted to hear from you. Also if you would like to consider writing a short article for the newsletter please email us with details: laila.guzadhur@niche.org.uk