



NEWSLETTER SEPTEMBER 2016

In this edition we report on news from partners of the Frailomic Initiative and MID-Frail study. This newsletter also provides a project status update for both studies and a list of upcoming conferences. After a busy period for MID-Frail, the Screening and Baseline visits have been completed and all the data have been monitored. We provide an update on the shipment of biobank samples to the laboratories for the Frailomic Initiative. Both projects are entering exciting phases both looking forward to finishing the next series of MID-Frail patient visits and obtaining results first sample assays in the Frailomic Initiative!

We hope you enjoy hearing about the recent events and news from the Frailomic Initiative and MID-Frail consortia. As always, please let us know if you would like to share any news in our next edition!

In this issue:

- Frailomic status update
- A guide to accessing the shared database
- MID-Frail news including Alannah's visits to the sites
- Publications update and conferences

Note: do not to share the contents of this newsletter with anyone outside the consortia as it contains confidential information that should only be available to Frailomic and MID-Frail partners (this newsletter will not be published on either of our websites).



Partner News

The Frailomic Validation Phase Begins

By Laila Guzadhur on behalf of Niche Science & Technology
(with thanks to Betty Davies Urizar)

The first half of 2016 marks an exciting, operational period involving the transportation of biobank samples from the cohorts. A lot of work has gone towards preparing the sample labels and organising the logistics for sample shipment. Samples from the SARDINIA cohort have been sent to the respective laboratories in the first week of May 2016 and at the time of writing this newsletter samples from the Toledo (ETES) and ENRICA cohorts have been scheduled for shipment. The required authorisation for transporting samples of the MAPT cohort is now in process. The MAPT cohort consists of 1680 frail, elderly subjects, aged 70 years or over. Good luck everybody!

The shared database continues to be updated and maintained by YouHealth. Partners have been able to access the database after signing the consent document or the reciprocal consent document. To help you get started with the database please follow the guide below.

a guide on how to access the Frailomic Database

by Assistant Professor David Gomez-Cabrero, Unit of Computational Medicine,
Karolinska Institutet, Center for Molecular Medicine, Karolinska University
Hospital, Stockholm

The path to establishing a complete, sharable version of the Frailomic data – including data harmonisation and database preparation across the cohorts – was long and required a considerable effort from numerous partners. Thank you to everyone involved! Finally the system is ready and working however, not everyone is aware of the process you need to follow to access the data. We would like to take this opportunity to provide some information and guidelines in this edition of the newsletter.

STEP 1

What data can be accessed and by whom?

There are specific rules about what data can be accessed by each partner:

- Every partner can access (and owns) the data they provided to Frailomic. For instance, a cohort partner will be able to access both original data and harmonised data; experimental partners will be able to access the data they generated.
- Any partner may request access to any other data. The process is fairly straightforward, access needs to be granted by the owner of a specific dataset of interest. Requesting partners are required to:
 - » Contact the owner of the data and discuss possible sharing of data, goals, etc
 - » Fill in a Consent Document (if you have not seen it before please contact frailomicproject@gmail.com) and return the signed document to frailomicproject@gmail.com and imad.abugessaisa@ki.se
- Finally, to ensure secure access, you will need to provide a permanent IP address to imad.abugessaisa@ki.se. If you do not know how to get a permanent IP address, please contact the IT team at your institution.

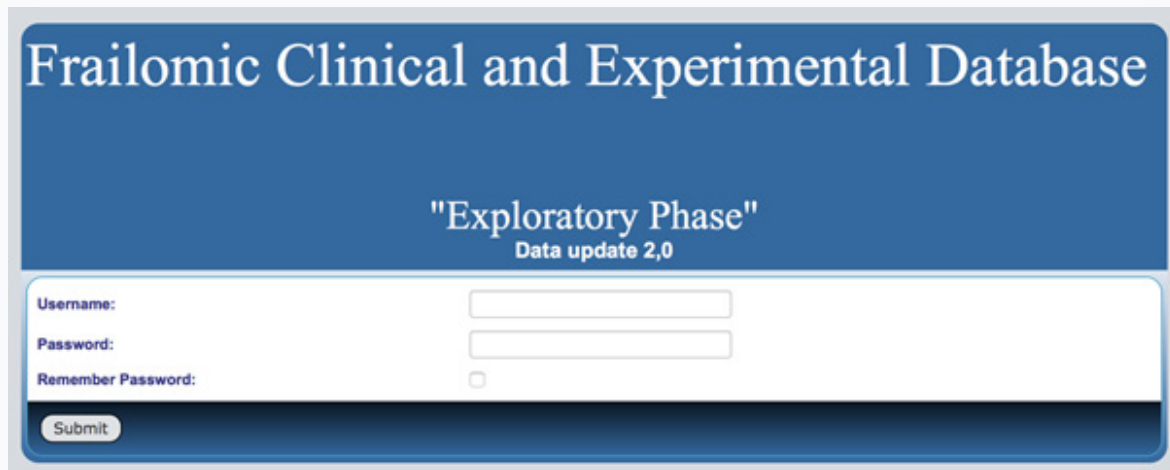
step 2 »

STEP 2

Now that I have filled in the required document how do I access the data from the website

<http://frailomic.cmm.ki.se> ?

Imad (imad.abugessaisa@ki.se) will contact you to provide you with a link to the database as well as a username and password. Please check it as soon as possible to ensure everything is working. An example of the database landing page can be seen below.



Frailomic Clinical and Experimental Database

"Exploratory Phase"
Data update 2,0

Username:

Password:

Remember Password: ☐

Submit

step 3 »

STEP 3

A few notes on the database content:

Depending on the rights granted to you, you will be able to access different parts of the Frailomic dataset. Some notes on the material:

- Harmonisation code-book: this includes a brief description of each of the harmonised variables. You will be able to see different versions. If this is your first time you only need to consider the latest version.
- Cohort data:
 - » Although xlsx format is not an optimal format for data sharing we have used this method to facilitate access to most partners. All files are compressed in zip format.
 - » You will find two versions of the cohort data: original data and harmonized.
- Experimental data: all files are gzipped and in csv formats. The data included in these files has been matched between laboratory and cohort codes. Individual data (cohort or laboratory) that could not be matched were excluded. There was some loss of data in this step and we would like to assure all partners that every effort was taken to maximise data recovery.

step 4 »

STEP 4

And finally some specific recommendations!

We would also like to add some extra notes on the data to add further value to the Frailomic database. These include:

- We recommend that the latest version of the harmonised cohort data is used for any analysis. The original data can be used, however any questions regarding the data should be directed to the cohort representatives
- We agreed to update the data every 6 months. We are currently at version 02. The updates are also documented and for every one of them we are sending an email to all partners
- If you identify possible errors (or question) regarding harmonisation, please report to david.gomezcabrero@ki.se but please be VERY specific, with clear examples. We do make mistakes, but we will need your help to clarify if it is a mistake or not
- If you have any other specific suggestions, please let us know and we can discuss on how to proceed

who to contact if I have problems »

Who do I contact if I have problems?

- If you have any questions on how to access the database or download the data, please contact imad.abugessaisa@ki.se.
- If you have any questions regarding the harmonisation, please contact david.gomezcabrero@ki.se.
- If you require specific documents, please contact frailomicproject@gmail.com.

This will always be a work in progress and we value any comments, feedback, recommendations and or requests (and always your patience!).

A final comment: **Happy Mining!** We encourage everyone to exploit this fantastic resource to help better characterise and define frailty!

David



SEPTEMBER 2016

Frailomic Meetings

Our next general Frailomic meeting will be in Mallorca on the 3rd–4th November 2016. Please confirm your attendance to Stefan and Betty by emailing them at frailomicproject@gmail.com

The Frailomic Initiative will be participating at the 21st International Association of Gerontology and Geriatrics (IAGG) World Congress of Gerontology and Geriatrics, which will be taking place in July 2017, in San Francisco, California. The consortium have been invited to take part in a workshop led by Dr Jeremy Walston of the Johns Hopkins University School of Medicine, clinical specialist in geriatric medicine. Dr Walston's research is focused on aging and frailty and his leadership and participation in committees of the American Geriatrics Society and review panels for the National Institute on Aging helps set the national aging research agenda. We are very excited to for the 21st IAGG congress. Please look up the website for further information. <https://www.iagg2017.org>

MID-Frail travels

Our clinical research associate, Alannah Symth describes her travels to the MID-Frail centres and the opportunity it provided to meet members of the team.

It has been a great experience working with the investigators and study teams in the countries I have been visiting while I hope to visit sites in the remaining European countries by the end of December. What a great team you all are.

So far, all of the Intervention Group sites in Sicily and Belgium have been monitored, and with Parma and Verona being monitored within a week, Italy will be fully complete by the end of July 2016.

Visiting the individual sites has provided me with allowed greater insight into how the study is progressing, and also allowed me to ascertain how the enjoyment of each patient is deriving from their participation.

Many of the sites randomized to the Intervention Group are reporting that patients have found bi-weekly visits too much of a commitment and this has resulted in a number of withdrawals. It is important for each of us to remember that our candidates often express a large numbers of concurrent morbidities, and that withdrawals are to be expected.

However it's great to hear that for many patients, visiting the site have managed to benefit from the social aspects. Many enjoy the time they get to spend with the study teams and other patients. One site in England has even reported a blossoming romance that has resulted from MID-

Frail visits! Social isolation is a significant risk factor for many pathologies prevalent in this population, so this added benefit should be viewed positively and embraced.

When monitoring University Hospital Naples, I met with Dr Anna Lombardi and Alessia Memmi, who, in conjunction with Prof. Nicola Ferrara, run the day-to-day procedures and visits for their site. As a number of the patients enrolled at the hospital need to travel considerable distances to attend the clinic, a special effort has been made by Anna and Alessia to respond to the patients concerns of the individual patients and we hope this has been served to minimise drop-outs that may otherwise have resulted from such a logistical challenge.

In July I also visited UZ Ghent in Belgium, where patients for three of the Belgian sites fall under the care of Stefanie de Buyser, Eline Meireson and Lore Vandaele. After 4 years devoted to MID-Frail, Stefanie is sadly leaving the study in September to pursue a master's degree in statistics. Stefanie's position will be filled jointly by Eline and Lore, who are both incredibly excited about their new positions and the opportunity that it will bring for them.

Bon voyage and the best of luck to Stefanie and also well done to Eline and Lore for their new roles in the coming year.



Research nurse, Alessia Memmi and Dr Anna Lombardi

Alannah

continued...

MID-Frail travels *continued...*

Having met and worked through the eCRFs with partners of the MID-Frail consortium, Alannah would like to thank everybody for their diligence when completing the data forms. Some common queries she has encountered include:

Common Queries

Screening and baseline visits have been completed, but it's worth noting the following points:

- Both brand names and generic names should be recorded for all concomitant medications
- The date '01-01-1900' should be used if start dates for concomitant medications are unknown
- For any concomitant medications initiated after study enrolment an associated adverse event record should be raised (this includes a change in dose of an ongoing medication)
- Ensure that the Medical History Form includes all conditions listed in the concomitant medication section of the eCRF
- Record haematocrit values as a percentage in the, and not in mmolL. For example: 0.342 mmolL should be entered as 34%
- Waist circumference must be recorded in cm's. Please ensure the withdrawal criteria at the bottom of the eCRF has been completed; even if the subject is not withdrawing please answer 'no' to the question 'is this page applicable?'

If you are not able to enter information, you can respond to any raised queries stating this or contact the team at Niche who will be available to help out.

MID-Frail project update

By Karen Chalk

Thanks to everyone who helped with the huge effort in recruiting nearly 1000 subjects for the MID-Frail study. It's been an intensely busy period!

The study will now finish by February 2017, with participants completing a 12, 18 or 24 month follow up visit. According to the recruitment dates, all participants in the project should be able to complete 12 months of follow up - the main outcome of the MID-Frail study. Participants who have already completed follow up visits beyond month 12, should have their final visits completed within the last 3 months of the clinical trial (between December 2016 and February 2017).

Those of you involved in with organising and conducting MID-Frail visits should ensure that procedures originally scheduled for Visit 8 are now performed at the participant's final visit to the site.

Further details can be found in the MID-Frail study protocol (please note this has been updated to Version 7, as of 30 June 2016), study procedures section. The main change from protocol Version 6 to Version 7 includes this finish date for the study and the subsequent changes to appropriate dates for last visits. Version 7 describes all procedures to be performed at all visits. Please also refer to this version of the protocol for any other queries and don't hesitate to contact the Niche team if you have any questions!

Thanks to everyone coordinating participant visits and we wish you all the best with your continued efforts towards a successful end of study visit. Due to your hard work we are in the fortunate position of the first batch of participants having completed their final visits!

Karen

Head of Clinical Project Management and Quality Systems, Niche Science & Technology

Publications

It's been an extremely productive period for both the Frailomic and MID-Frail Initiative. The first half of 2016 has been an exciting time for partners of the Frailomic Initiative, in particular – with progress having been achieved with several publications.

Works in development

Four applications for approval have been submitted to the Frailomic Intellectual Property Committee (IPC) and all have obtained approval for development from the consortium IPC

- The first application to be approved was from Stefan Walter. This planned manuscript will describe the risk factors of frailty from an –omic approach. The working title is 'The –OMIC Risk Factors of Frailty' and the authors will be taking data from Phase 1 of the Frailomic Initiative and reporting on the associations between risk factors for frailty and the various levels of frailty
- The second manuscript to obtain IPC approval is being led by David Gomez-Cabrero. In this manuscript the authors will be reporting the factors involved in the diagnosis of frailty. The methods and results towards the generation of the minimal models that have been identified from work undertaken during Phase 1 will be presented
- Mariam El Assar and colleagues have conducted an evaluation of gene expression in frailty. Their work has involved investigations into genes implicated in cellular response to oxidative stress, inflammation, vascular physiology and hypoxia. This work is now being developed into a manuscript by the team and is the third manuscript to be approved by the IPC this year. We are looking forward to having this published!

- The fourth manuscript is a description on the challenges involved in multi-cohort studies. This will be relevant to several other studies and we wish Imad Abugessaisa of the You Health team and his co-authors the best in developing this manuscript

Dr Jose Viña and his team continue to drive the publication of 'mRNA analysis in centenarians reveals specific patterns associated with control of apoptosis and cellular senescence'. Following submission to Nature Communications, additional experiments were performed. However, the manuscript was unfortunately rejected in peer review. The authors submitted the manuscript to Aging and are waiting for a decision. Niche Science & Technology have also been working with the authors of an epidemiological review of frailty. Sophie Regueme and colleagues continue to revise the SENSOLE part 1 manuscript. We would like to remind MID-Frail and Frailomic partners to follow the publications process. Please send the completed application forms, with your intentions to publish, to Laila at Niche who will coordinate review of your application to the IPC.

If you have had manuscripts published or attended conferences which have in part arisen from using MID-Frail/Frailomic resources – please also remember to acknowledge the supporting project and keep the Niche team updated.

Publications continued...



Call for More Frailomic Publications

A word from the Frailomic Senior Scientific Project Manager: Stefan Walter

We have only received four IPC applications to write manuscripts based on Phase 1 of the FRAILOMIC Project. We strongly urge you to submit your ideas to the IPC so that we can publish our research findings. If you have any doubts about the epidemiological / biostatistical methods that should be applied to answer a specific research question please do not hesitate to get in touch with me (stefanfrailomics@gmail.com) in Madrid. For any questions regarding the IPC process please write to Laila Guzadhur at Niche (laila.guzadhur@niche.org.uk). Laila is also available to provide writing and/or editorial assistance with any of our Frailomic projects.

We are more than happy to help you complete the IPC form. In addition, it is important to say that limited resources for statistical analysis should not inhibit you from formalising your ideas. We have the resources to help you get started and I am sure during the Mallorca meeting in November 2016 we can come up with a plan to assure that all analyses that are deemed relevant can be published.

Best Regards

Stefan

Frailomic Senior Scientific Project Manager

Publications continued...

Published Works

Congratulations to the Evercyte team on publishing their work in Aging Cell. The manuscript 'Secreted microvesicular miR-31 inhibits osteogenic differentiation of mesenchymal stem cells' was accepted for publication in March 2016. Weilner et al., 2016 report elevated levels of the microvesicle – miR-31 in the plasma of elderly and osteoporosis patients and identify senescent endothelial cells as a potential source of secretion. To enjoy reading more, please find the article here: <http://www.ncbi.nlm.nih.gov/pubmed/27146333>

Catherine Feart and her team have published the paper 'Higher Protein but Not Energy Intake Is Associated With a Lower Prevalence of Frailty Among Community-Dwelling Older Adults in the French Three-City Cohort'. The study by Rahi et al., 2016 assessed the protein intake of older adults in the 3C cohort and found that high protein intake was associated with lower frailty prevalence. The original study was published on 01 July 2016 by the Journal of Post-Acute and Long-Term Care Medicine (JAMDA; volume 17, issue 7, 672e.7–e11) and can be obtained at the journal website ([http://www.jamda.com/article/S1525-8610\(16\)30127-X/abstract](http://www.jamda.com/article/S1525-8610(16)30127-X/abstract)). Congratulations to the authors: Berna Rahi, Zoé Colombet, Magali Gonzalez-Colaço Harmand, Jean-François Dartigues, Yves Boirie, Luc Letenneur and Catherine Feart. According to Altmetric, the original article has been tweeted and read several times on Mendeley!

The Frailomic Initiative has been featured in the EU science, research and innovation magazine –Horizon. Laila asked the editorial team at Horizon magazine, whether they would be interested in publishing a report about the study. After initial

Publications continued...

discussions the magazine identified an independent journalist who conducted an interview with Professor Leocadio Rodríguez Mañas. The magazine article also discusses the EU-funded Frailsafe project, which studies elderly people in their normal situation rather than in clinical settings. The study is led by Professor Vasileios Megalooikonomou at the University of Patras, Greece and intends to better understand frailty in relation to biological, environmental, and behavioural factors, by using wearable sensors and using a data mining approach.

The Horizon article featuring Frailomic and Failsafe has now been published in the magazine and we thought that you might like to read it. Please enjoy reading the article at:

http://horizon-magazine.eu/article/frailty-indicators-could-help-prevent-problems-ageing_en.html

Congratulations to Professor Sinclair and Professor Rodriguez-Mañas who have recently published a review article in the Canadian Journal of Diabetes, which featured the MID-Frail study. [http://www.canadianjournalofdiabetes.com/article/S1499-2671\(15\)00632-2/abstract](http://www.canadianjournalofdiabetes.com/article/S1499-2671(15)00632-2/abstract)

Research at the Cardiovascular and Nutritional Epidemiology Group (CNEG) at the Universidad Autónoma de Madrid has focused on the impact of lifestyle (e.g., diet, physical activity, sedentary behaviour) and environmental factors (e.g., heavy metals, passive smoking) on the risk of frailty. This is directly relevant to the main goal of the Frailomic Initiative, which aims to establish if -omic biomarkers can improve the diagnosis, risk and prognosis assessment of frailty beyond current methods of lifestyle and clinical factors that are easily and routinely measured in older adults. To this end, the CNEG has used data from the Seniors-ENRICA cohort and has worked collaboratively with many partners of the Frailomic consortium that also lead several cohorts: the Toledo Study for Health Aging (Professor Rodriguez-Mañas, Dr. Francisco José García and colleagues), the Bordeaux 3-City cohort (Dr. Catherine Feart and colleagues), the AMI cohort (Dr. Berna Rahi and colleagues) and the InCHIANTI cohort (Dr. Stefania Bandinelli and colleagues).

Professor Fernando Rodriguea-Artalejo of the CNEG and colleagues have published 'Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults'. The authors report an association of fruit and vegetable consumption with a lower short-term risk of frailty and stronger associations when intake equates to three portions of fruit and two portions of vegetables. The article can be found at Am J Clin Nutr 2016 104: 132–142 (<http://ajcn.nutrition.org/content/104/1/132.full.pdf+html>). In addition to this manuscript, research and collaborations at CNEG has resulted in the following publications:

- García-Esquinas E, et al (2015). Diabetes and Risk of Frailty and Its Potential Mechanisms: A Prospective Cohort Study of Older Adults. Journal of the American Medical Directors Association, 16 (9) 748–754
- García-Esquinas E, et al (2015). Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. Obesity, 23(4) 847–855
- García-Esquinas E, et al (2015). Association of lead and cadmium exposure with frailty in US older adults. Environmental Research, 137, 424–431
- García-Esquinas E, et al (2015). Exposure to secondhand tobacco smoke and the frailty syndrome in US older adults. Age, 37(2)
- García-Esquinas E, et al (2016). Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults. American Journal of Clinical Nutrition, 104(1) 132–142
- García-Esquinas E, et al (2016). Housing conditions and limitations in physical function among older adults. Journal of Epidemiology and Community Health, jech–2016–207183
- Graciani, A, et al., (2016). Ideal Cardiovascular Health and Risk of Frailty in Older Adults. Circulation. Cardiovascular Quality and Outcomes, 9(3) 239–45.
- Lana, A, et al, (2015). Dairy consumption and risk of frailty in older adults: A prospective cohort study. Journal of the American Geriatrics Society, 63(9) 1852–1860

Publications continued...

- León-Muñoz LM, et al (2015). Patterns of alcohol consumption in the older population of Spain, 2008–2010. *Journal of the Academy of Nutrition and Dietetics*, 115(2) 213–224
- León-Muñoz LM, et al (2014). Mediterranean Diet and Risk of Frailty in Community-Dwelling Older Adults. *Journal of the American Medical Directors Association*, 15(12) 899–903
- León-Muñoz, LM et al (2015). Major dietary patterns and risk of frailty in older adults: a prospective cohort study. *BMC Med*, 13(1), 11
- León-Muñoz, LM, et al (2016). Alcohol drinking patterns and risk of functional limitations in two cohorts of older adults. *Clinical Nutrition* (ahead of print)
- Martínez-Gómez D, et al (2015). Physical Activity, Sitting Time and Mortality in Older Adults with Diabetes. *International Journal of Sports Medicine*, 36(14) 1206–11
- Martínez-Gómez D, et al (2015). Nonexercise Cardiorespiratory Fitness and Mortality in Older Adults. *Med. Sci. Sports Exerc*, 47(3) 568–574
- Orozco-Arbeáez E, et al (2015). Habitual chocolate consumption and 24-hour blood pressure control in older adults with hypertension. *J Am Geriatr Soc*. 63(12) 2637–2639
- Ortolá, R, et al (2016). Patterns of alcohol consumption and health-related quality of life in older adults. *Drug and Alcohol Dependence*. 159, 166–173
- Ortolá, R, et al (2015). Patterns of alcohol consumption and risk of frailty in community-dwelling older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 71(2) 251–258
- Rodríguez-Artalejo, F & Rodríguez-Mañas, L (2014). The frailty syndrome in the public health agenda. *Journal of Epidemiology and Community Health*. 68(8) 703–704
- Soler-Vila, H et al (2016). Contribution of health behaviours and clinical factors to socioeconomic differences in frailty among older adults. *Journal of Epidemiology & Community Health*. 70:354–360

Members of the Intellectual Property Committee



The Frailomic consortium welcomes Associate Professor Lino Sánchez Ibarzábal as a newly appointed IPC member. He is partner and technical director at iDeTra and consults in research and development and technology transfer. Professor Ibarzábal replaces Cristina Catalina as a representative iDeTra on the Frailomic IPC.



Professor Lino Sánchez Ibarzábal



MID-Frail also welcomes two additional members to the consortia IPC: Professor Mirko Petrovic from Ghent University and Professor Ivan Bautmans of Vrije Universiteit Brussel, whose research focuses on inflammatory processes involved in muscle weakness and sarcopenia.



Professor Professor Mirko Petrovic



Professor Ivan Bautmans

Conference List

We hope the conference list in our last MID-Frail/Frailomic Newsletter was of some help. As discussed last November the newsletters will feature a list of upcoming conferences that may be of interest you. Although some deadlines for abstract submission may have passed, the details are provided here if you wish to attend. If there are any other conferences that are not on this list but you find relevant, please do let us know and we'd be happy to include this.

Before writing abstracts for submission, don't forget to lodge your intentions to publish to the IPC 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**
23–27 March 2017, Florence (Italy). Abstract submission open from 01 October 2016, deadline 13 January 2017. <http://www.wco-iof-esceo.org>
- **International Conference on Frailty and Sarcopenia Research (ICFSR)**
27–28 April 2017, Barcelona, Spain. Abstract submission deadline 30 November 2016. <http://www.frailty-sarcopenia.com/>
- **International Association of Gerontology and Geriatrics (IAGG) World Congress**
July 2017, San Francisco, California. Late breaker abstract submission opens 15 December 2016, deadline 15 February 2017
- **IANA (International Academy on Nutrition and Ageing)**
23 July 2017 at Moscone Center West in San Francisco, USA. Deadline for abstract submission passed
- **21st International Congress of Nutrition**
15–20 Oct 2017, Buenos Aires, Argentina. Abstract submission opens 03 October 2016
- **European and Word Congresses of Geriatric Medicine and Gerontology (EUGMS)**
5–7 October 2016, Lisbon, Portugal. Deadline for abstract submission passed. <http://www.eugms.org/2016.html>
- **Society for Free Radical Research Europe**
8–11 June 2016: Budapest (Hungary), at the Danubius Thermal Hotel Helia. Deadline for abstract submission passed. <http://sfrr-e-2016.hu>

Future Newsletters

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