Notes

What: **Annual meeting, NH Hotel Schiphol Airport, The Netherlands**
When: **27 September 2013**

Attendees: Leonard van den Berg, Julian Grosskreutz, Orla Hardiman, Markus Weber, Christoph Neuwirth, Susana Pinto, Francois Salachas, Janine Kirby, Vincenzo Silani, Nicola Ticozzi, Barbara Thuss, Martin Turner, Jan Veldink, Alice Vajda, Hessel Fransen, Anne Visser, Martijn van den Heuvel, Markus Otto, Taha Omar, Cristina Moglia, Jesus S. Mora

Actions

	What	Who	When
1	Distribute notes of meeting and slidepack	Barbara	11-10-2013
2	Launch SOPHIA website and include new projects (e.g. ECAS) and SOPs DNA sampling & storage, serum collection	Barbara	31-10-2013
3	Arrange combined JPND project meetings for 2014 & 2015	Leonard/Barbara	13-12-2013
4	Arrange Progeny cost sharing and invoices	Barbara	01-11-2013
5	Set up consortium for clinical research and biomarkers (WP4)	Leonard	May 2014
6	Finalise core clinical dataset, ECAS, MUNIX, MRI, staging ALS, neuropathology (others?) in Progeny and provide login details	Jan/Barbara	29-11-2013
7	Write SOP for use of core clinical dataset	WP1/Jan	15-11-2013
8	Distribute SOPs for collection and storing of biological material (e.g. DNA)	WP1/Barbara/Jan	31-10-2013
9	Adjust URL for the Progeny database	Jan	
10	Develop data sharing agreement to be signed by each partner prior to access to Progeny database	Jan	15-11-2013
11	Complete translation and validation of ECAS – Sharon Abrahams to contact interested partners and provide information	ITA1, POR1, FRA, TUR, POL, SPA	28-02-2014
12	Liaise with Ammar, Orla and Adriano to produce SOPs on systems for staging ALS (Ammar's and Adriano's system and ALS-FRS) and distribute to interested SOPHIA members; Arrange data fields in the Progeny database	Leonard/Barbara	29-11-2013
13	Liaise with JPND regarding length of JPND acknowledgement in publications	Barbara	31-10-2013
14	Chase FRA, POL, SWI, GER1-Ulm for feedback on neuropathology protocol	Robin/Barbara	11-10-2013
15	Distribute SOP on DNA sampling and storage for genetics project	Jan	31-10-2013
16	Perform MRI variability study and share results	Julian, Martijn	31-12-2013
17	Deliver SOPs for data upload and handling	Julian	31-12-2013
18	Check whether MUNIX spreadsheet is the same as the Progeny data fields to be able to import data directly	Christoph	31-10-2013
19	Set up 1-day MUNIX training course in St. Gallen and invite SOPHIA members	Christoph	31-10-2013
20	Set up needle EMG survey	Hessel	15-11-2013
21	Communicate messages from Magdalena's group to all	Barbara	31-10-2013
Further specific actions within WPs will be communicated through the WP leaders			

WP5 Project management (Leonard van den Berg)

- SOPHIA is recognised as a JPND success story and highlighted on the JPND website and in the upcoming JPND newsletter (October 2013)

Notes

- SOPHIA annual JPND reporting deadline is 31 January 2014; Input from WP and project leaders will be requested by 13 December 2013 by Barbara
- SOPHIA website will go 'live' in October
- JPND requires annual meetings for all its projects. As SOPHIA partners also participate in several other JPND projects ('ALS-CarE' led by Orla Hardiman, 'STRENGTH' led by Ammar Al-Chalabi, 'VD_ALS_EU Strategies and interventions for vital decisions in Amyotrophic Lateral Sclerosis in different European countries' led by Dorothée Lulé), it would be time-efficient to join these meetings and have a larger (2-day) meeting once a year. This also allows establishment of links between the projects (e.g. staging in ALS in SOPHIA and CarE), involvement of non-funded partners in related projects and new input into on-going research.
  The kick-off meeting for ALS-CarE will be Jan/Feb 2014 and might link up with the kick-off of STRENGTH, which is due to start in February 2014. This might be too early for SOPHIA however. Leonard/Barbara will discuss with Orla, Ammar and Dorothé and come up with a proposition to all SOPHIA partners for meetings in 2014/2015. Potentially a short 1-hour meeting might be planned during the International Symposium on ALS/MND in Milan in December with SOPHIA partners present there to discuss this. (There will also be an ENCALS meeting in the afternoon of 5 December in Milan).

No.	Institution	Country	PI (SOPHIA)	SOPHIA	CarE	STRENGTH	VD_ALS_EU
1	UMC Utrecht	NET	Leonard van den Berg	x	x	x	
2	Katholieke Universiteit Leuven	BEL	Wim Robberecht	x	x	x (Walter Sermeus)	
3	Assistance Publique Hopitaux de Paris	FRA	Francois Salachas	x			
4	University of Ulm	GER	Markus Otto / Albert Ludolph	x		x (Jochen Weishaupt)	x (Dorothee Lule)
5	Jena	GER	Julian Grosskreutz	x			
6	Trinity College	IRE	Orla Hardiman	x	x		
7	University of Turin	ITA	Adriano Chio	x	x	x	
8	Istituto Auxologico Italiano	ITA	Vincenzo Silani	x		x	
9	Medical University of Warsaw	POL	Magdalena Kuzma-Kozakiewicz	x			x
10	Instituto de Medicina Molecular	POR	Prof. Mamede de Carvallho	x			
11	Instituto de Tecnologia Quimica e Biologica	POR	Julia Costa	x			
12	Servicio Madrileno de Salud	SPA	Jesus S. Mora	x			
13	Kantonsspital St. Gallen	SWI	Markus Weber	x		x	
14	University of Istanbul	TUR	Yesim Parman	x			
15	University of Sheffield	UK	Pamela Shaw	x	x (Chris McDermott)	x	
16	Oxford	UK	Martin Turner	x			
17	King's College London	UK	Ammar Al-Chalabi		x	x	
18	Charité – University Medicine Berlin	GER	Thomas Meyer		x		
19	Techn. Univ. of Munich	GER	Gian Domenico Borasio		x		
20	University of Ulm	GER	Gisela Badura Lotter				x
21	Umea University and Sunderby Hospital Luleå	SWE	Ursula Werneke				x
22	INSERM U930 - Université François Rabelais	FRA	Philippe Corcia			x	
23	Karolinska Institutet	SWE	Ye Weimin			x	

- With combined JPND meetings more multidisciplinary professionals could be invited and better dedicated workshops can be planned. This will also help the SOPHIA project to disseminate its results to the rest of the ALS/MND and wider ND community.

WP4 Open innovation platform (Leonard van den Berg)

- How do we make sure SOPHIA efforts continue after the project officially finishes? How do we maintain funding? Biomarkers are becoming very important, also in clinical research. This goes for imaging (MRI), neurophysiology (MUNE/MUNIX) as well as wet biomarkers (CSF, blood). An idea is to establish a consortium of ALS centres for clinical research (trials) and biomarkers. This trials consortium should be ready for new calls in the future as part of Horizon 2020. All participating (European) centres use European standards for EMG, MRI, clinical data, staging in ALS, etc. (as developed by SOPHIA and Euro-MOTOR) and a structure for continuous quality control as developed by SOPHIA, which can be attractive to companies developing new drugs. This should be communicated to the pharmaceutical industry: The trials consortium could offer its experience and several services in executing more efficient and enhanced ALS clinical research, and this way maintain itself.
- It was suggested this could all be synchronised under ENCALS. However, in the long term it should be possible to include centres from outside Europe, for example Australia and Asia. The consortium should be able to teach and support and collect data together with centres outside Europe.
- The Edinburgh Cognitive and behavioural ALS Screen (ECAS) is becoming the global method for measuring cognitive function. Training sessions/webinars, validation, certification, etc. are up and running. ECAS is a good example of how to validate and harmonise a specific method and/or analyse over multiple ALS centres in an efficient way. Other centres should be able to see what is happening and be able to participate. Therefore ECAS should also be promoted via websites (SOPHIA website, consortium website) and other platforms.
- Possibly NISALS could be included in the platform/consortium, as they are developing and using parts of SOPHIA as diagnostic control.
- Funding for online databases is not a big problem whilst grants are running, but what happens after? E.g., NISALS currently has a resource barrier and needs to develop a new management structure in order to be able to continue work in the future. A lack of funding of NISALS creates some problems in this regard. Using a third party is no option as this is very expensive. Would centres be prepared to pay for access to data, like NISALS, or for a quality check to improve their own performance? Probably not, centres only perform specific MRIs for a project like NISALS when they're already well at it.
- Cooperation and sharing of data is the only way forward (e.g. MRIs, whole genomes, etc.); multicentre approaches are key. However, it takes time for people to realise this and to start trusting and sharing their data: In genetics and GWAS, centres needed to collaborate. Finally, 2 out of 8 centres wouldn't join the collaborative effort and it took 3 years to publish. The same is now happening with exome sequencing. Policy should be that individuals can obviously extract data for their own publications first, but then share it with larger groups and enlarge the total information base.
- Plan: Build consortium -> arrange funding -> integrate with smaller groups/efforts like NISALS. The consortium will be there by May 2014!
- SOPHIA has funding so will be able to use it to contribute to European-wide collaborations which can then been built upon for the future.

Experience national funding agencies (all)

A short inventory was held about the experiences of all SOPHIA partners with their local funding agencies: Whether they encountered specific problems with reporting, whether they received their

funding, etc. All seems to be going smoothly, some funding agencies require annual financial reports, others are happy with the annual JPND scientific report only. Some partners requested prolongation of the funding into the 4th year (SOPHIA is a 3-year project); this is usually accepted. If any problems occur, the SOPHIA project coordinator should be contacted. They can provide help and involve the JPND secretariat if needed.

WP1 Core clinical dataset & Progeny (Jan Veldink) – *See slidepack for more information*

- A core clinical dataset has been defined. Feedback from SOPHIA partners has been obtained and discussed: Awaji criteria and region spreading fields will not be added to the core clinical dataset nor to the MUNIX data tab. ECAS will be added and replace the FAB. (Unfortunately ECAS cannot replace FAB anymore in the Euro-MOTOR project, as this project has progressed too far already.) Data fields for diagnostic delay will be added. A "progression rate" field as suggested by Martin will be added.
- What is 'bulbar'? Phenotyping could be done better. Write 'Phenotype at onset'. Currently Adriano's clinical phenotypes have been used, Martin suggested to include the different regions according to El Escorial (upper and lower motor neuron signs), which will be added.
- An SOP will be developed by WP1 which explains how to fill in the core clinical data fields, e.g. to define what 'Date of onset' is.
- SOPs for collection and storing of biological material (serum, urine CSF, DNA, RNA, fibroblasts) are complete and to be disseminated to all partners.
- Progeny has been set up for collection of the core clinical data and all biomarker data. Guidelines will be provided to all users on how to set up and use the database, e.g. how to log in, what security measures have been taken (compliance to US Dept of Health and Human Services and to European guidelines), rights of the users (admin vs. researcher), etc. See the slidepack for more details on Progeny.
- The Progeny database is flexible, excel or access databases can be imported so people do not have to actively maintain double databases. UMCU will support SOPHIA members with the importation of data. When importing data, it is key to check for duplicates within the input data first. Each entry gets a global ID assigned automatically by Progeny. Additional individual name/ID numbers can be added. See the Progeny guidelines for more details.
- One can query within own data but it also technically possible to query across centres as well as projects. Security settings can be adjusted for this, but this will only be done very carefully and after extensive consultation with all partners involved.
- All SOPHIA members will get login details to Progeny as soon as the final tweaks have been made to the core clinical dataset, following the feedback from SOPHIA members on the first draft. A MUNIX data collection sheet has been built in Progeny as well, in cooperation with WP3b leaders. It will be opened up to all WP3b participants shortly as well.
- The project coordinator has suggested to share the running costs of Progeny: UMCU initially spent €66,000 to set up Progeny and spent another €11,680 for upgrading of the system to allow more users. There is an annual servicing cost associated with the use of Progeny in the amount of €13,499. UMCU has taken a 3-year subscription to these services, resulting in a discount of €7,192. Splitting the servicing costs among the SOPHIA partners comes down to a total contribution of €2,379 per partner, for which separate invoices can be arranged. The EU will not directly fund this but national funding agencies will. All SOPHIA partners present agreed to share these costs. Solutions for future cost sharing (>3 years) or when additional projects join Progeny will be dealt with at that time. Some partners indicated they have to check whether they can free up the money from their allocated budget. Payment arrangements will be made by the project coordinator.
- The URL for the Progeny database will be adjusted to a more general name.

- Discussion about sharing of data and authorship policy: SOPHIA needs to define an authorship policy up front, also in view of the trials consortium that may be set up. Should a centre contribute a minimum number of samples to be included within the consortium? The issue with NISALS is that people are not contributing samples without being co-authors on a publication, or being in a 'senior author' list. Could we use single-name authors, could we use no-named authors and only name the consortium? Or will this prevent people from putting in any effort and performing analyses? Ownership of data is needed and a decision taken on how the authorship will be defined prior to analysis. Large meta-analysis studies need to be outlined first by the individual and proposed to the consortium, this includes the authorship policy for the specific project. Then each member can decide whether they want to contribute their data and be involved in the analysis project or not. Analyses of the collected data by external parties should be possible as well, if the consortium members agree with the proposal. A time limit could be set for use of the data, so people don't sit on the data without publishing. Decisions will be tailor-made depending on the specific goal of a future project, and a Steering Committee derived from the SOPHIA partners will be put in place to decide on these issues. A good example is the FTLD consortium in Germany.
- Jan will draft a data sharing agreement (DSA) for the SOPHIA partners, in part based on the example of the German FTLD consortium (www.ftld.de), to be signed by each partner prior to gaining access to Progeny database.

WP1 ECAS (Orla Hardiman) – *See slidepack for more information*

- At the SOPHIA interim meeting at ENCALS in May 2013 it was decided to implement ECAS in SOPHIA as neurocognitive changes are evident in ALS and need to be measured – third domain following upper and lower MN loss. Orla's data suggests this is related to outcome.
- The screening can be performed by a nurse in 15-20 minutes, though with some SOPHIA partners report it takes more time, up to 30 minutes. ECAS needs to be done face-to-face rather than over phone or as web-based analysis.
- A publication on ECAS by Sharon Abrahams is now available as free download ('Screening for cognition and behaviour changes in ALS'). ECAS guidelines and the screening are available to all and the screen has been translated into Dutch, Italian and German.
- ECAS data for validation is collected by Orla, Leonard van den Berg (Utrecht), Vincenzo Silani (Milan), Ammar Al-Chalabi (London), Martin Turner (Oxford), Albert Ludoplh (Ulm), Markus Weber (St. Gallen); 40 patients and 40 controls should be collected by end of Sept. 2013.
- Since the SOPHIA interim meeting Adriano Chio (Turin), Mamede Carvalho (Lisbon), Francois Salachas (Paris), Yesim Parman (Istanbul), Magdalena Kuzma-Kozakiewicz (Warsaw) and Jesus Mora Pardina (Madrid) have shown interest and are translating ECAS into Portuguese, Spanish, Turkish and Polish. Aim is to complete translation and validation by the end of February 2014. Sharon will be asked to email these new participants with all information and a link to the online training video. An SOP on how to translate ECAS will be developed and distributed.
- All final data goes to Sharon Abrahams so it can be analysed in a systematic manner.
- NEALS is now interested in using this method – Merit Cudkowitcz' group is using it.
- All training and screening material will be available on the SOPHIA website once it is launched in October (to be organised by Barbara together with Sharon Abrahams).

WP1 Staging in ALS (Leonard van den Berg)

- A paper has been published by Ammar Al-Chalabi regarding staging in ALS. The proposed system is different from ALS-FRS and based on El Escorial criteria: How many regions are involved, PEG, ventilation, etc. Staging is related to survival, quality of life, health costs.

- Adriano Chio has proposed a similar system based upon ALS-FRS.
- Ammar requests the SOPHIA group to validate his staging system prospectively.
- Julian mentioned some issues regarding the onset of stage 2 in Ammar's system; some feel this stage follows stage 3 instead of the other way around.
- There are some limitations as to using non-invasive ventilation as a parameter for staging, because local health policy can dictate when this occurs, rather than the patients stage being similar across Europe.
- Pharmaceutical companies like Biogen and GSK are very interested in development of a staging system.
- Leonard suggests SOPHIA validates both systems (Ammar's and Adriano's) and the ALS-FRS to find out which one is better. For this, multiple volunteers were present in the SOPHIA group. Leonard will liaise with Ammar, Orla and Adriano to produce SOPs for use by those interested and will arrange data fields in the Progeny database to collect the staging data.

WP1 Neuropathology (Janine Kirby) – *See slidepack for more information*

- Robin Highley received feedback from several neuropathologists of the participating SOPHIA partners on the neuropathology draft proposal. Those who have not responded yet will be chased by Barbara & Robin (e.g. FRA, POL, SWI, GER1-Ulm). Their feedback is needed by Friday 11 October, or they can confirm that they agree.
- A pathology database is being set up. A separate box is required to report that there is other documentation available on a subject, e.g. the anonymised post-mortem report, quantitative measure of inclusions, etc. It will be difficult to actually attach these documents in Progeny (Barbara to find out!).
- Discussion regarding acknowledgements: Barbara to liaise with JPND to see if it is possible to reduce the acknowledgements in publications if they were funded by SOPHIA, STRENGTH or CarE, as it currently is a very long list. Members should report to the SOPHIA consortium when they encounter any problems with journals not accepting long lists of funders.
- All SOPHIA publications should be mentioned on the SOPHIA website.

WP1 DNA sampling and genotyping (Leonard van den Berg)

- A quick round-the-table showed that most SOPHIA members are collecting DNA from both FALS and SALS patients and controls.
- An SOP on DNA sampling and storage is available from/being prepared by the Euro-MOTOR effort and will be distributed.
- Leonard is setting up and executing a whole genome sequencing study combined with a large GWAS ('project MinE'): 15,000 ALS cases & 15,000 controls in the GWAS and 15,000 ALS cases & 15,000 controls for whole genome sequencing. The GWAS is ongoing, regarding the whole genomes 600 cases and 400 controls have been sequenced. Another 1000 genomes (400 cases & 600 controls) will follow soon. On most ALS patients environmental data is available as well.
- To achieve this project a multicentre international approach is needed. Leonard invites all interested ALS centres to participate in this project and to make it one ground-breaking international effort to find the genetic basis of ALS.
- Biogen is currently exome sequencing a 1000 ALS genomes. Leonard is trying to get them to participate and therefore has a meeting with Biogen in November.
- There are two Dutch ALS patients who initiated the project together with Leonard and who are assembling the funds for this research together with the ALS Foundation of the Netherlands. They are promoting this project worldwide in order to create awareness and get people involved.

- The required budget for this project is substantial. In each country, participating scientists should apply to the national funding bodies to do whole genome sequencing of a certain number of samples, which will then form part of the collaborative European sequencing study. The Dutch ALS Foundation and the two Dutch ALS patients will be able to assist the national funding bodies in the fundraising campaign for this research.
- A promotion video was shown at the meeting, more details about the project will be shared with all SOPHIA members in due time.

WP2 Wet biomarkers (Markus Otto) – *See slidepack for more information*

- Aim of the workpackage is to create a system to harmonise sampling methods.
- Task 1, deliverable 1.1: Consensus on protocols used for biosampling and which biomarkers to measure; there is an SOP for lumbar puncture and CSF collection. They will be distributed by Markus.
- Task 1, deliverable 1.2: A common neurochemical data set has been set out through "reverse" round-robin. New measurements to test the system of harmonisation of wet biomarkers involve neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNfH).
- Task 1, deliverable 1.3: Internal and external quality control – Data summarised in the ALS & FTD paper which is under review (Reviewers comments received by Markus Otto this week – some revision of text and justification required.)
- Abeta and Tau appeared quite variable in both ALS cases and controls and across centres. It is thought that a review of clinical data by different clinicians may be the issue.
- Phosphorylated NFs showed differences between ALS cases and controls, but levels were variable across centres.
- Task 2, deliverable 2.1 (training): Report of the 2-day course in Ulm on 25 & 26 September 2013: Courses should be in native language and continue beyond Sophia. These can be national courses as well as joint courses with BiomarkAPD. It was suggested to have some form of accreditation. There should be online material, e.g. webinars and a place to communicate the standardization process -> Launch of working group 'Clinical Neurochemistry and CSF'. They already have a webpage domain set up. It should be a joint collaboration between SOPHIA and BiomarkAPD, as well as other interested parties, including MS researchers. Links to and from the SOPHIA website.
- Task 2, deliverable 2.2 (monitoring): Decision is pending
- Task 2, deliverable 2.3 (integration of round-robin system in biosampling protocols): SOPHIA partners are requested to measure neurofilaments (NfL, pNfH) in CSF using a kit sent out by Markus to see what the inter-laboratory variability is. Markus will send an email to all to see who is interested.
- Task 3: A biobank has been established for test material (CSF & serum). A discussion on RNA/DNA is needed. Reverse round-robin: Centres are invited to participate and send CSF of 5 ALS cases and 5 controls to Paris and Ulm (no neurodegenerative disease or meningitis cases).
- Some patients are not detected by C9orf72 repeat PCR, so need to do southern blot to be definite.
- Other biomarkers? TDP43 was suggested but appears not ready for harmonisation yet.
- An SOP for serum collection is available from Euro-MOTOR and will be published on the SOPHIA website. Currently there are differences in SOPs for serum between ALS centres. Is SOPHIA aiming to lay down 1 SOP for all centres to use? Will all centres abandon their own ways and start following this SOP? We should first investigate how different centres collect

serum and what differences this gives in the results. After that we could choose the most optimal protocol and recommend it to all centres.

WP3a Imaging (Julian Grosskreutz) – *See slidepack for more information*

- The MRI repository (NISALS) is working, data is being collected, need to encourage last centers to upload data. Upload strategies of participating centers need to be reviewed, they cause much need for manual correction. 50% of centers do not upload DICOM data, so the original acquisition parameters are lost for the variability source analysis. The WP will establish a SOP for data format and upload procedure. The WP will develop a standardized de-anonymization routine while preserving other data in headers. Data ID translation tables are being defined together with Utrecht. Process of ID verification should be controlled and checked by the uploading centers. Robust SOPs for data upload and handling are expected by the end of the year.
- Results of the variability study are due by the end of 2013, the study will be performed by Jan Kassubek (DTI), Julian (T1/VBM/VBI) and Martijn (cortical thickness).
- Quality control: Analysis can indicate how a specific centre's MRIs compare with the imaging data submitted by other centres. This information is confidential and only for the specific centre. It should also provide some clues regarding how results may be improved.
- How to reduce the amount of MRI data to make it useful as a biomarker in trials? MRI data is looked at by physicists to check for variability within the scan, the resolution (in terms of the thickness of slices), etc. However, whether these results correspond to the centre's ability to detect ALS is a different question. The analysis has to be independent of the software used to sample the data.
- Quantitative measurements need to then be cross-correlated with other clinical data. If the overall aim is that MRI becomes a biomarker for clinical trials this data should link to ALS-FRS at the minimum, and ideally also to other clinical characteristics, genetics and wet biomarkers. It would therefore be good to know the genotype of all patients of which we have MRIs, so we should obtain DNA samples. However, ethics committees may raise issues. We do have ALS-FRS data for most of these patients.
- Using the data in the Jena MRI repository: The strategy is that individuals can put in a bid for a project to research a specific hypothesis. This bid will be reviewed by the potential project partners that provide their data for the project. If accepted the project can start and the data will be shared. There may be project-specific requirements for partners, like a minimum of 20 scans per centre, or requirements for the project initiator, like only those centres which have submitted at least 20 images are allowed to analyse the data.
- Data protection: It is essential that every single MRI is anonymised, as each scan is automatically labelled with the patient's name. The data also needs to be "de-faced", as certain anatomical hallmarks allow recognition.
- Current status of MRI collection: 937 MRI scans so far; 509 ALS, 415 controls (T1, T1.5, T3 and resting state fMRI taken). The barrier for multicentre data analysis is 20 cases and 20 controls. No clinical information is required at the moment so C9orf72 status of the patients is unknown. There is major variability between centres as protocol and type of scanner and shades of grey, etc. are all different among the participating centres. These systemic differences cause the loss of any ALS-specific features that should make MRI a biomarker for ALS.
- Prospectively, we need to make C9orf72 status a compulsory item – at least collect the DNA! – perhaps also link with ECAS?
- Deliverable 1: Complete
- Deliverable 2: Ongoing, integration of Progeny and the MRI repository

- Deliverable 3: Repository is now closed for cross-sectional analysis of initial data
- Deliverable 4: What is the best protocol? And will all centres comply once the best protocol is found/developed? All scanners are different, is I at all possible to develop 1 protocol? Software settings can solve many differences and therefore 1 protocol is still a possibility. Can we use existing protocols like those from the ENIGMA Network or the ADNI (Alzheimer's Disease Neuroimaging Initiative) consortium? ADNI is old, and new sequences are constantly being developed, so the result of this deliverable may be basic recommendations for imaging parameters which are likely not correctable by software routines (spatial resolution isometric, signal-noise-ratio, movement artefacts).
- Deliverable 5: This deliverable is a challenge because of the current low overlap of available data. Orla and Markus W. may have datasets that can be used here, and further efforts can be undertaken to encourage multimodal data collection of the same patients in SOPHIA centres.
- Deliverable 6: Is this deliverable valid, is this part of SOPHIA, the actual implementation and collection of data? We might be able to use data already uploaded in NISALS which is the international ongoing initiative SOPHIA integrates into in MRI studies.
- Deliverable 7: Ongoing

WP3b MUNIX (Markus Weber, Christoph Neuwirth) – *See slidepack for more information*

- There have been three training courses so far, in St Gallen and Dublin; SOPs have been established.
- Each investigator studies 4 patients twice, results are reviewed by Christoph; Centres can only continue the longitudinal study if variability less than 20%.
- The majority of centres involved have ethical approval granted, and half of these have passed the investigator reliability test.
- WP3b is slightly behind schedule due to ethical approval process and setting up the Progeny database for MUNIX; Once these two processes are completed significant progress can be made.
- The MUNIX datasheet has been set up in Progeny, but needs final tweaking. After that it can be opened up to all participating investigators so data can be assembled, monitored and analysed.
- At the moment, individuals enter MUNIX data into a dedicated spreadsheet, from which data can be easily imported into Progeny. MUNIX participants have to be aware though that they may be using an old spreadsheet, e.g. the colleagues in Portugal. Those using the old spreadsheet should adjust it or copy their data into the new spreadsheet. For more details, Christoph can be contacted.
- Core clinical data should be assembled in parallel with measuring MUNIX. Therefore both data sheets in Progeny should be finalised a.s.a.p. and login details should be provided to all investigators. They could then feed results directly into Progeny. Until then, investigators can keep on using the spreadsheet and send these to Jan, who will import into Progeny (e.g. results from Portugal – Susana). However, the core clinical data set in Progeny does probably not correspond to the clinical data on the MUNIX EXCEL spreadsheet that is currently used. Suggestion: If direct import is not possible, those centres which have generated data have to enter the data into Progeny themselves manually.
- A test/retest is done every 6 months. Data from participating centres is checked for reliability before being entered into Progeny by sending it to Christoph or Christoph checks the data once they have been entered already. The latter would imply that anytime someone enters data, Christoph needs to be informed. Data sharing should be allowed to achieve this.

Christoph will be functioning like a monitor and will check the test-retest measurements and the longitudinal data for consistency and give clearance or approval of the data.

- Risks of MUNIX: Results of the variability tests so far show that it is crucial to optimize the CMAP amplitude as variability of MUNIX is mostly determined by CMAP variability. The CMAP reading in a previous MUNIX trial in one centre was so poor it almost ruined the entire dataset. Large variability in measurement results is possible, especially if inexperienced personnel is performing the measurements. This is why the inter- and intra-rater average variability should be less than 20%. A simple CMAP is most critical for overall performance, see also the study by Neuwirth et al, 2011.
- MUNIX reliability is trainable! Over 4 training sessions, variability reduced from 21 to 11%. It is extremely helpful to show MUNIX examiners in hands-on sessions the typical sources of errors that are avoidable and to sensitise them.
- Patients are their own control over the course of the disease; from normal control level down to zero.
- Decision to set up another 1-day MUNIX training course in St. Gallen on Friday 22 November for those who did not attend a course yet. Following this course the examiners could then do (after some training at their centre) the test-retest examination in 4 healthy volunteers (e.g. lab staff) and qualify for the longitudinal data collection. The training session is mandatory; investigators cannot progress with a longitudinal study without attending at least one course and passing the variability test first. This will avoid easy mistakes and will reduce variability between centres. If required, particular issues can be targeted at the upcoming training course to reduce variability. Christoph will arrange a course and send invitations to MUNIX examiners who want to collect longitudinal MUNIX data.
- The SOPHIA website will mention results from the tests and indicate which centres are certified for MUNIX.
- If variability between centres remains high at the end of all training courses and tests, it might be that MUNIX is simply not a feasible biomarker in a multicentre setup.

General discussion and way forward

- UMCU neurophysiologist Hessel Franssen had some questions regarding performing needle EMG: His experience is that there is more variability between neurophysiologists than patients, examiners are doing the needle EMG in different ways. His suggestion is to perform a survey with all SOPHIA partners to see how people investigate a muscle with needle EMG (questionnaire), and develop some rules/a protocol for this, as textbooks and papers do not provide any guidelines on this. The neurophysiologists present concurred and Hessel will initiate this survey.
- Electric Impedance Myography (EIM) is very useful for patient follow-up. Any reason why it didn't take off in Europe? Julian suggests that muscle ultrasound may be more informative for some areas. Muscle ultrasound may replace needle EMG in the future for diagnosis, especially for certain muscles. Even fasciculations and fibrillations can be seen on muscle ultrasounds.
- Update activities Poland (Magdalena Kuzma-Kozakiewicz – conference call): Unfortunately the presentation by Magdalena was cancelled. Her slides will be included in the meeting slidepack distributed along with these minutes. By email, Magdalena indicated that the two most important messages from the SOPHIA colleagues in Poland are:
    - They require help in introducing voxel based morphometry (protocols, best softwares, etc.)

- They propose a comparison of protocols (efficacy, house-keeping genes expression, time to reach a given cell density with different protocols) between all the centres using EBV-immortalized lymphocytes (Sheffield, Ulm, Warsaw, others?)

These matters will be communicated once more in a separate email to all PIs and WP leaders.