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Workshop report

48th ENMC International Workshop: Drug Trials and Clinical Research in ALS
12–14 January 1997, Naarden, The Netherlands

Professor Alan Emery (Budleigh Salterton, UK) welcomed 24 participants from the US and eight European countries who met in Naarden (NL). Vincent Meininger (Paris), Michael Swash (London) and Vianney de Jong (Amsterdam), the present European Members of the World Federation of Neurology (WFN) Subcommittee on ALS Trials, had called for this ENMC Workshop with the intention of starting to establish a European constituency for the WFN Subcommittee and moving towards founding an inclusive European consortium for explanatory or therapeutic trials and for collaborative research.

The Friday afternoon session, chaired by Wim Robberecht (Louvain) and Jean Pouget (Marseilles), made an inventory of the common European assets (Moderator: Wim Robberecht) and problems (Moderator: John Wokke, Utrecht). A discussion on the structure and goals of a European consortium was moderated by Jean Pouget. Pamela Shaw (Newcastle upon Tyne) summed the session up as follows:

1. Main assets: a sufficiently large population that has a rather equitable access to health care. Most European countries have good population registers; distances between patients’ residencies and centers with adequate ALS expertise are usually small. For pharmaceutical industries, conducting therapeutic trials in Europe is relatively cheap.

2. Main problems: the population is divided over about 14 different health care systems. Quality of life scales, like the Sickness Impact Profile, must be validated in at least 10 languages. Because of price setting by the European governments, pharmaceutical industries often reap greater benefits by operating in the large and open US market.

3. An open structure that accommodates existing networks and coordinates efforts is to be preferred. None of the participants favored a consortium that might regulate access to trials, regulate the size of local consortia or attempt to replace existing networks.

4. The goals of a European consortium appeared to include the science of motor neuron degeneration, the search for better treatment and the promotion of better patient care. Acquiring a small but independent trial bureau is a medium to long term goal. The consortium will not engage in training clinicians in epidemiology or biostatistics; it aims at transparent forms of interaction with industry. High priority will be given to early diagnosis, to trial design and to selection of appropriate therapeutic agents.

5. The scarcity of academic clinical epidemiologists and biostatisticians and of clinical pharmacologists, one of each being present, remains a matter of concern.

6. The participants were well aware that they had no mandate to take decisions on behalf of all European ALS investigators.

At the end of the session Frank Baas (Amsterdam), also acting on behalf of Nigel Leigh (London), reported on the failure of the European Biomed 2 application for Familial ALS. A rewritten application has been submitted for the Rare Diseases Program. The outcome will be known by the end of 1997. A serious search for local funding has begun and the participant centers appear determined to move ahead despite limited present resources.

The Saturday program was also attended by four representatives from the pharmaceutical industry: Dr Alan Doble (Research Director, Paris) and Mr Anthony Kievid (Pharmacist, Amstelveen, NL) of Rhône-Poulenc-Rorer; Dr Colin Markland (Director, Cephalon Europe, Guilford, UK) and Mr Michael Mellink (Director, Cephalon Benelux, Soest, NL) from Cephalon-Chiron.

The morning session, chaired by Pamela Shaw and Maria de Sales Luis (Lisbon) addressed problems in international collaboration (Speaker: Vincent Meininger), included a critical discussion of the WFN protocol for the American-European combination trial with Riluzole (Ril) and insulin-like growth factor-1 (IGF-1) (Speaker: Robert Miller, San Francisco CA), presented an overview of the practical requirements for participating in the WFN-originated website for paperless trials (Speaker: Benjamin Brooks, Madison WI) and ended with a discussion, moderated by Robert Miller and Benjamin Brooks, on how to build a successful consortium.
1. The participants agreed that international collaboration increases the complexity of a study by an order of magnitude, but is worth the extra trouble because it tends to augment the validity of the study results.

2. The WFN diagnostic criteria did not meet with opposition. A case was made in favor of including rapidly progressive suspected and possible ALS cases, perhaps to be distributed over the study arms by stratification prior to randomization. The participants agreed that patients should enter trials as early in the disease as possible.

3. No progress was made in solving the difficult question of ownership of trial data.

4. Maximum voluntary isometric contraction (MVIC) myometry has been demonstrated superior to handheld myometry, according to publications in US physiotherapy journals. Because MVIC of the legs exhibits great variability, the Ril-IGF-1 combination study protocol limits itself to MVIC of the arms.

5. Participants were encouraged to put themselves on the address list of the WFN website, where a European page will be open.

6. Successful American consortia have organized themselves around trial opportunities. Individual centers may participate in more than one consortium. The administrative structure limits itself to a secretary and a database. Contact is maintained by phone conferences and face-to-face meetings, the latter usually organized as satellites to major neurology venues. Training of coordinators and myometrists and supervision of data quality have proven necessary. No simple solutions have been found for removing centers that do not maintain agreed upon standards, nor has the decision to enlarge a well running consortium always proven easy.

The Saturday afternoon session, chaired by Reinhard Dengler (Hannover) and Isobel Illa (Barcelona) included a critical review of existing trial protocols (Speaker: Patrick Bossuyt, Amsterdam), a report on the logistics of introducing MVIC (Speaker: Sebastian Conradi, Stockholm), an update on the European Health Profile Study (HPS) (Speaker: Michael Swash), an overview of therapeutic agents (Speaker: Gilbert Bensimon, Paris), and an update on forthcoming combination trials with Ril (Speaker: Dr Adam Doble, Rhône-Poulenc-Rorer, Paris), IGF-1 (Speaker: Dr Colin Markland, Cephalon, Guilford, UK) and Sanofi SR57746A (Speaker: Vincent Meininger as Chairman of the Trial Steering Committee).

1. Because no spectacularly effective medications are expected, it is advisable to validate the major components of ALS trial methods in neuromuscular diseases that are curable.

2. Methods ascend stepwise from measuring the disease mechanism to assessing the quality of life and, as they do so, become more vulnerable to outside disturbances.

3. Collating large amounts of disparate data into megascores or megaslopes leads to opaque results that may mask clinically valuable information. Except death, all present trial end points are surrogate end points.

4. MVIC myometry is worthwhile, but requires a full-time myometrist. Megascores decline in a linear fashion, but strength of individual muscles does not always do so.

5. The double blind period of trials of agents that seem about to become available in the near future may be estimated to require about 9–18 months.

6. If HPS data will only be acquired from patients who do not participate in a therapeutic trial, worries about the representativeness of the results are warranted.

7. The major categories of eligible drugs are antiexcitotoxic agents, antioxidants, trophic factors, and inducers of trophic factors.

8. Rhône-Poulenc-Rorer and Cephalon are seriously moving forward to a Ril-IGF-1 combination trial. Two derivatives of Ril are under study but do not seem about to become available for testing in ALS in the near future. Perhaps, a combination trial of Ril and N-acetylcysteamine may be considered.

9. The first future international combination trial is Ril and Sanofi SR 57746A. In countries where patients are eligible for Ril therapy, this combination study will be an add-on trial.

10. The participants voiced their concern about the early access program for IGF-1 and wished to urge colleagues in Europe not to start patients on IGF-1 without a more detailed protocol for monitoring patients, despite requests from individual patients. Drs Gian Borasio and John Wokke will develop a protocol and liaise with representatives of Cephalon.

Several important decisions were made at the end of this session:

1. The participants decided to establish an ENMC ALS Study Group.

2. They agreed with nominating Vincent Meininger Chairman, Pamela Shaw Secretary and John Wokke Treasurer and ENMC liaison.

3. They agreed on founding an inclusive European ALS Consortium that will be the constituency for representing Europe at the WFN Subcommittee on ALS Trials.

4. Regionally, each participant will send Pamela Shaw names and addresses of all neurologists who do serious work on ALS.

5. At the November 1997 Glasgow International ALS Symposium, all European neurologists with a genuine interest in ALS will be invited to join the European Consortium and advised to become members of the WFN Subcommittee on ALS Trials.

6. The ad hoc elected Board of the ENMC ALS Study Group will be proposed as Board of the European Consortium. Elections will be held in Glasgow.
Because there is no constitution or bylaws, the only reasonable way of forging ahead is to invite all neurologists mentioned sub 4 above, to propose countercandidates.

7. The participants were in favor of working within the scope of the WFN Federation of Clinical Trials Consortia but felt no urgent need to formulate a constitution and bylaws.

The Sunday morning session, chaired by John Wokke and Orla Hardiman (Dublin) addressed the ethics of further placebo-controlled ALS trials (Moderator: Reinhard Dengler), discussed the preferred trial methodology (Moderator: Patrick Bossuyt) and the preferred trial participation (Moderator: Gilbert Bensimon).

1. The participants were unable to attain a uniform stance on future use of placebo, because of variable availability and divergent opinions on the efficacy of Ril. Participants from countries where Ril is being reimbursed by the health care system tend to proceed from the assumption that, for the time being, Ril is standard ALS treatment.

2. They will strive to maintain a sensible balance between explanatory and therapeutic trials.

3. Michael Swash will call for a training course in clinical epidemiology and biostatistics at a meeting of the European Federation of Neurological Societies. Patrick Bossuyt has offered to organize that course.

4. In general, participants favored large trials using relatively simple methods; they realized that trials of intrathecally administered growth factors may require a small scale approach.

5. The ENMC ALS Study group has listed five projects:
   (a) **MVIC.** Organizers: Vincent Meininger, Michael Rose (London).
   (b) **HPS.** Organizers: Michael Swash and Gian Borasio (Munich).
   (c) **FALS, molecular and cellular studies.** Organizers: Nigel Leigh, Frank Baas and Wim Robberecht.
   (e) **Standards of care.** Organizers: Maria de Sales Luis, Orla Hardiman and Gian Borasio. The participants welcomed collaboration with the US groups working on standards of care. Specific topics included: (1) end of life issues; (2) percutaneous endoscopic gastrostomy; (3) symptomatic therapy; (4) communication of the diagnosis; and (5) assisted ventilation.

6. Pamela Shaw will take charge of keeping the Study Group informed by means of a newsletter. She has distributed our first letter of January 1997.

7. John Wokke will be in charge of organizing future ENMC ALS Workshops. Two of them have already been proposed: (a) Pamela Shaw will prepare a workshop on glutamate in ALS. (b) Dirk Troost (Amsterdam) will prepare a workshop on neuropathological ALS criteria.

Professor Alan Emery closed the Workshop at noon.

**List of participants**

G. Bensimon, France
G. Borasio, Germany
P.M.M. Bossuyt, The Netherlands
B.R. Brooks, USA
W. Camu, France
A. Chiò, Italy
S. Conradi, Sweden
R. Dengler, Germany
A. Doble, RPR, France
A.E.H. Emery, ENMC, The Netherlands
O. Hardiman, Ireland
I. Illa, Spain
J.M.B.V. de Jong, The Netherlands
A. Kievid, RPR, The Netherlands
A. Ludolph, Germany
C. Markland, Cephalon, UK
V. Meininger, France
M.P. Mellink, Cephalon, The Netherlands
R.G. Miller, USA
J. Mora, Spain
G. Ochs, Germany
J. Pouget, France
W. Robberecht, Belgium
M. de Sales Luis, Portugal
P. Shaw, UK
V. Silani, Italy
M. Swash, UK
J.H.J. Wokke, The Netherlands

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