RESEARCH AUSTRALIA
CLINICAL TRIALS NETWORK

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13 August 2015

Dear Sir/Madam,

Thank you for providing the opportunity to comment on the Adoption or Non-Adoption of European Guidelines. We specifically comment here on the proposal to adopt the European Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis.

The MS Research Australia Clinical Trials Network was established to facilitate the clinical trials process for MS in Australia and New Zealand and increase awareness and access to clinical trials for people with MS. The MS Research Australia Clinical Trials Network is a central point of information for people, investigators and companies interested in participating in or conducting an MS clinical trial and for news about MS clinical research and trial activity. The MS Research Australia Clinical Trials Network is led by an Executive Committee of highly experienced MS specialist neurologists and clinical triallists (more information www.mstrials.org.au).

Modelled on other successful clinical trials networks, our aim is to:

- Improve the opportunity to participate in trials for both patients and neurologists
- Increase communication and interaction between trial sponsors, trial sites and patients
- Increase patient awareness about trials
- Enhance trial sponsors' awareness of Australia and New Zealand's capacity to undertake MS trials
- Assist with the development of both industry sponsored and investigator initiated studies

We welcome the provision of clear guidelines that will assist in the development and conduct of clinical trials for MS in Australia. Having clear guidelines that are consistent with global trials will also be advantageous for the development of local trials, particularly investigator-led trials, for MS medications. This will ensure that investigators have access to the appropriate information to assist in the development of their trials, and that ethics committees are also well informed about the appropriate design of clinical trials for MS.

On the whole we feel that the European Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (the Guidelines) are appropriate for Australian circumstances, are in line with global knowledge of MS and globally accepted standards for the conduct, assessment and validated outcome measures for MS trials.

However, there a number of areas in the Guidelines that warrant careful consideration and are perhaps points that should be regularly reviewed to ensure that the Guidelines remain current.

For example, there are several items in the Introduction that we feel perhaps do not reflect the most recent state of knowledge on MS. This includes the statement that 'Within ten years more than 50% of patients who suffer from a relapsing-remitting form eventually develop sustained disability with or without superimposed relapses; this form is called the secondary progressive multiple sclerosis' – the most recent data on the development of secondary progressive MS for patients *under treatment* suggests it will be reached in 25 years from onset for men and 30 years for women (Ribbons et al., PLoS One. 2015; 10(6): e0122686).

Data is also emerging on the markers that distinguish 'the transition from RRMs to SPMS'.

The assertion that 'In primary progressive multiple sclerosis the inflammation is cortical and more diffuse' implies that there is no cortical activity in RRMS, which is also not the case.

Given that data is rapidly emerging in these areas, it will be imperative to revisit the Guidelines regularly to ensure that they remain current.

We note in section 3. that these Guidelines should be read in conjunction with a number of other European Guidelines. Care will need to be taken to ensure that these guidelines are also adopted, or alternative Australian Guidelines are specifically referenced for the purposes of the Australian use of the Guidelines. This is particularly important in reference to the three Guidelines listed in section 3. that pertain to biosimilar medications as this is currently a topic of discussion and review within Australia – the consensus in Australia, currently, appears to be that biosimilars should not be 'substituted', but rather a medication 'switching' approach should be taken in consultation with the prescribing doctor.

In section 4. (Specific considerations when developing products for the treatment of multiple sclerosis), we would suggest that section 4.1, regarding the possible endpoints for treatments of acute relapses, ought to also include the stabilisation of symptoms beyond the '3-6 months' stated in the Guidelines. Additionally, in section 4.2.1 the duration of studies for treatments for relapsing remitting MS would ideally be a minimum of three years rather than 'approximately 3 years'

We also question the statement that 'The usefulness of developing products for patients with a "real" CIS that will not be classified as MS or inclusion of RIS (radiological isolated syndrome) is considered doubtful.' Studies of medications for real CIS have already been conducted and are considered to be highly relevant. If no trials on RIS or real CIS are done then no knowledge can be gained on how early we should treat people with CIS/MS.

In section 9.2 the Guidelines state 'For chronic treatment, it is expected that at the time of marketing authorization, safety data of at least 2 years are available for a meaningful number of patients.' We consider that this may not be long enough to detect safety concerns due to lack of immune surveillance as previous drug development studies have shown.

We also feel that pregnancy registries 'should' always be considered, rather than 'may' be considered.

We understand that the points covered in our submission are relatively minor in the context of the otherwise comprehensive and thorough Guidelines and we note them more as points for careful

consideration and future reference, rather than a suggestion that the Guidelines should not be adopted.

As discussed at the outset, the adoption of globally accepted, clear guidelines, will be extremely advantageous both for the TGA in assessing clinical trials data for MS medications and for investigators developing clinical trials within Australia. The Guidelines will facilitate a robust clinical trials process for MS medication in Australia that maintains the safety of patients, while affording them the opportunity to access cutting edge therapies.

Yours faithfully,

Associate Professor Jeannette Lechner-Scott
Chair, MS Research Australia Clinical Trials Network Executive Committee