Submission of comments on ' (EMA/.../...) Clinical investigation of medicinal products for the treatment of Multiple Sclerosis (Rev.2).

Comments from:

Professor George Ebers, MD MA FRCP FMedSci. Nuffield Department of Clinical Neurosciences, Level 3, West Wing, John Radcliffe Hospital, Oxford OX3 9DU

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INTRODUCTION AND PERSONAL STATEMENT

I am a Professor of Neurology at the University of Oxford. I am now Emeritus Professor having come from Canada 14 years ago to be Head of Department here. I have spent my professional career working on Multiple Sclerosis, a disease which has been in my family. See Google Scholar link: http://scholar.google.co.uk/citations?user=tDNCWBYAAAAJ&hl=en

When I started out as a post doc at the Rockefeller University in New York, Multiple Sclerosis was widely believed to be a viral disease and then as today there were many proposed therapies none of which had stood the test of time or had actually been replicated.

There was no putative effective treatment on the usual outcome measures until 1992 when the results of the original Interferon (Betaferon) study were announced. Here a reduction of MRI lesions and a modest reduction in relapses was found. There was no significant effect on the disability measures used but these were all short term measures.

Despite the frail clinical trial measures used, the trial results led to approval of Beta Interferon by the FDA. Now some 25 years have passed since the initial trial was started, and it seems appropriate to make some commentary on what has happened in the intervening years. The entire story of therapy and drug approval is within my personal experience from the start to the present.

I was one of the principal investigators in the original Betaseron study, and was the principal investigator of the PRISMS study. Both were placebo-controlled trials of beta-interferon in MS. However soon after these studies were complete, I found it increasingly difficult and eventually impossible to go along with what was happening. I stopped participating in trials because I had concerns about the ethical issues involved. I still do. The basic presumption is that putting patients in studies when the outcomes have not been validated is not appropriate unless it is made clear
what the limitations are. In brief, risk should not be taken when the evidence for efficacy is not based on a comprehensible and validated outcome.

GATEKEEPING FOR PATIENTS: HOW PATIENT ADVOCACY HAS BEEN ERODED

The evolution of MS therapies now highlights and invites scrutiny of what are meant to be the main safeguards of patient welfare or shall we say patient advocacy in the process of finding effective therapy.

Patient advocacy (traditionally standing between industry on the one hand and patient welfare on the other) has been the province of the following stakeholders. This role has been substantially eroded in the past few decades as follows:

1. ACADEMICS.

Academics have been the main bulwark against exploitation of patients. This has been true historically, and the ethos of the medical profession has for thousands of years been one in which doctors are taught, expected, and relied upon to be patient advocates. Furthermore because of the personal contact, education, and tradition of physicians, both public and private entities have been comfortable with the physician being the main protector of patient welfare in the matter of therapeutics. No-one is better suited to weigh the evidence and compare risk and benefit. Over the last generation, things have changed in medicine in general and there is no clearer example of the process of change than what has happened in the field of Multiple Sclerosis.

Academics were faced with a dilemma in the late 1980's. It had become clear that several western governments discovered they could lighten their healthcare/research budgets to a very large degree by offloading the responsibility for clinical trials to drug companies. This task they took up with relish and they may have been influenced by major drug companies’ donations to political campaigns not to mention other activities with political parties. For decades interactions of academics with industry had been frowned on or proscribed. Previously, public granting agencies/charities had played an integral role in the evolution of efficacy determination. What happened to disturb this balance had not been a gradual process but in MS it had developed relatively abruptly over a few years. There was little or nothing really to debate formally about MS therapeutics until the early 1990's. There was no effective treatment other than symptomatic.

I can speak for most of the investigators at the onset of the interferon trials that almost no-one expected Interferon, the first approved therapy, to work. This is documented objectively in the Jekyll Island referendum which took place in the late 1980s. Here 60 or 70 clinical trialists in MS were asked what they thought were the most promising therapies – more about this later.
Interferon was selected last among 13 options as something which had promise for efficacy for Multiple Sclerosis (See appendix A) in 1988 and next to last for apparent evidence to slow disability.

Table 2. Apparent ability to slow progression of multiple sclerosis in the short term

<table>
<thead>
<tr>
<th>Treatment (ranked)</th>
<th>Responses</th>
<th>Moderate efficacy</th>
<th>Considerable efficacy</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methylprednisolone alone</td>
<td>Moderate efficacy</td>
<td>25 (40)</td>
<td>29 (47)</td>
<td>54 (87)</td>
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<td>2. ACTH</td>
<td>Moderate efficacy</td>
<td>39 (63)</td>
<td>10 (16)</td>
<td>49 (79)</td>
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<td>3. Prednisone</td>
<td>Total lymphoid irradiation</td>
<td>36 (58)</td>
<td>8 (13)</td>
<td>44 (71)</td>
</tr>
<tr>
<td>4. Azathioprine plus corticosteroids</td>
<td>Cyclophosphamide plus plasma exchange plus corticosteroids</td>
<td>35 (56)</td>
<td>3 (5)</td>
<td>38 (61)</td>
</tr>
<tr>
<td>5. Total lymphoid irradiation</td>
<td>Cyclophosphamide induction</td>
<td>23 (35)</td>
<td>13 (21)</td>
<td>36 (56)</td>
</tr>
<tr>
<td>6. Cyclophosphamide plus plasma exchange plus corticosteroids</td>
<td>Cyclophosphamide induction plus cyclophosphamide maintenance</td>
<td>19 (31)</td>
<td>13 (21)</td>
<td>32 (52)</td>
</tr>
<tr>
<td>7. Cyclophosphamide induction</td>
<td>Cyclophosphamide induction plus cyclophosphamide maintenance</td>
<td>22 (35)</td>
<td>8 (13)</td>
<td>30 (48)</td>
</tr>
<tr>
<td>8. Cyclophosphamide induction plus cyclophosphamide maintenance</td>
<td>Cyclophosphamide plus plasma exchange plus corticosteroids</td>
<td>18 (29)</td>
<td>11 (18)</td>
<td>29 (47)</td>
</tr>
<tr>
<td>9. Cyclosporine A</td>
<td>Beta interferon</td>
<td>19 (30)</td>
<td>1 (2)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>10. Beta interferon</td>
<td>Cop-1</td>
<td>14 (22)</td>
<td>1 (2)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>11. Cop-1</td>
<td></td>
<td>10 (16)</td>
<td>3 (5)</td>
<td>13 (21)</td>
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The original data from these two studies (initially surprisingly showing relapse rate reduction efficacy) were never in the hands of the investigators. Many of us felt that the regulatory agencies would police the results. The PRISMS study of Interferon confirmed the original Interferon Berlex-Schering results (the first approved for “course altering” MS treatment) but it was not possible to make either company carry out studies aimed at longer term outcomes. Having spent nearly 30 years studying the natural history of the untreated disease, I knew that the longer term outcomes were what really mattered. Several companies actively resisted even carrying out follow-ups of the original trial patients, notably with Interferons. It took several years before studies were done in
progressive MS. This was disturbing, even more so when we learned that the FDA had insisted these followups be done.

When the obvious was not being done, I pressured companies into doing studies on the development of progressive Multiple Sclerosis which was clearly the key outcome responsible for the vast majority of medical, social and economic impact of MS. Neither company wanted to do it. They said privately that they had won approval and were selling lots of drugs so a progressive study could only hurt them. When these were in fact done, they were completely negative without any hint of efficacy (see progressive MS trials) so they were right about this. This ethos of putting the welfare of patients second spread quickly to some academics who became experts on the commercial rivalries at the expense of demanding to see the primary data and maintain their roles are patient advocates.

At that time I decided I would be in no further trials unless I had access to the primary data. This arose from experiences in one of the progressive trials, in which the company conducting MS trials had behaved with gross dishonesty. There have been at least three such occurrences in my experience, and in no case was there public exposure. In one case fraudulent changes to the raw trial data were carried out at the behest of the company, according to at least three internal sources.

2. THE GRANTING AGENCIES

Ordinarily, granting agencies provide a measure of advocacy for scientific merit and for patient interests. Their review process provides a type of control of behaviour or standard. However with the outsourcing of clinical trial grant funding to industry, this option was very largely conceded. Nothing more needs to be said but this contributed in a major way to trials being completely controlled by industry. In MS there are essentially no investigator-driven trials now.

3. THE JOURNALS

At one time academic journals could similarly provide a process of peer review as a requirement of publication in Lancet or NEJM e.g. protecting patients’ needs and welfare. This meant some kind of quality control. But what was once an objective process no longer pertains or has been severely eroded. For many years, granting agencies, journals and academic departments have had reluctance to enforce or control what surely must be obvious to anyone who has any sense of conflict of interest. What has happened has been very much like taking your favourite pet to the veterinarian and discovering he (the vet) moonlights as a taxidermist.
To repeat, in none of the pivotal MS trials leading to approval have the primary data been in the hands of the investigators as far as I can tell, and they surely have not been available to the public or to interested academics. All primary analyses have been done by industry statisticians. However, reading the papers that have been published in high profile journals one would never know this to be the case. Authors commonly put their names on papers they have not read, written or have analysed the data. (See Hinchliffe inquiry testimony of the Lancet editor.)

Particularly egregious has been the behaviour of the New England Journal of Medicine and the Lancet. We gradually became aware that a main source of income (perhaps the main one) for these 2 journals actually comes from industry. Industry purchases reprints for industry-funded articles that these journals publish and distribute them to doctors at various company-run venues. The reprint business is transacted at a staggering premium over what it costs to print these articles. In some cases the income from this has actually gone into the pockets of editors – at least I am so told for the New England Journal of Medicine. I understand, although I have heard only third hand, that Marcia Angel resigned her post as Editor of the New England of Medicine over this kind of issue.

In any event, trying to quantitate this, we have attempted to gauge the proportion of overall income which comes from selling reprints ( in the case of one MS paper I know, it was perhaps a penny to print and the journals were charging 50 dollars per copy).

We recently asked the BMJ, the New England Journal of Medicine and the Lancet to give us data on their income from industry-paid reprints. The BMJ was clean, the NEJM told us to get lost, and for the Lancet - probably by accident, a junior employee sent us the Excel spreadsheets for all the papers they have sold reprints for over the past many years. I have been told internally from the Lancet that they are under huge pressure from Reed Elsevier who owns them to generate income from these reprints.

We recently published our analysis of data we were able to obtain (Handel et al, Appendix B).This was all very disturbing.

This is only part of the story but illustrates how the journals have disabled and to a significant degree corrupted themselves, thereby neutralising their traditional capacity of being honest brokers and patient advocates. There can be no better illustration of this problem than by looking at the papers on Multiple Sclerosis that have been published in the last decade. There are several trials, all meaninglessly brief in duration, and which enunciate no new principle nor any new methodology, which have found their way into leading articles in the Lancet. This has occurred despite overwhelming reservations about the outcome measures, the data not being in the hands...
of the investigators, and their translation into clinical practice. The MS reviewers for the Lancet are
chosen, I have been told without concern for possible conflicts.

These occurrences have also disabled the usual processes in academic medicine in a disturbing
way. Several of the individuals who are senior authors on these papers have been promoted to the
rank of professor at universities based on high profile publications of this type. The promotion
committees are often far behind the realities, unaware of the money changing hands in favour of
lead investigators and more importantly their departments. Naively, many universities have taken
such high profile publications and their citations as indicators that the investigator is of such high
quality that industry would select them for conducting their trials.

In fact, nothing could be further from the truth in MS. Industry tends to select people to be principal
investigators partly because they perceive they have a sufficiently high profile in the community to
sway opinion but they are more discerningly selected for being pliable, unwilling to rock the boat,
and susceptible to pressure over principle. The key dealbreaker for industry is being willing to
speak up for the truth - is selected against. This has led to medical meeting after medical meeting
mostly now funded by industry) in which so called high-profile investigators list their conflicts of
interest on a slide which is left on the screen for less than a second. For many of these
investigators in the MS field the industrial conflicts individually number over 30 companies. They
routinely state they have no conflicts because they work for many competing companies. This is
clearly untrue and can be for example illustrated by the apparent collusion of MRI centres in
promoting MRI as an outcome, a notion which benefits all MRI academic sites. The collusion also
allows the income to be maximised.

In one particularly egregious example of academic industry conflict of interest/dishonesty, a former
student who moved to a drug company, was asked to draft a contract for a consultation agreement
with the head of department at a leading European university. The student wound up resigning
after the contract was completed. The student felt the details were intolerable and could not be
lived with. In brief 250,000 USD/year was to change hands and be paid into a bank account, not in
the academic’s own country, for the deliverable. Amazingly it was spelled out in the contract that
the investigator provide information on the activities on the other 2 competitor companies on
whose Advisory Board he sat.

THE OUTCOMES IN MS

As the appended Jekyll Island referendum indicates, prior to the Interferon trial no-one thought
relapses in MS were a particularly good outcome measure (ranked last in credibility). Indeed there
has been nothing subsequently which has established their validity. But MS relapses became the
outcome many drug companies found they could beat. If anything, their validity has been further discredited by the fact that the number or relapses, easily and ubiquitously counted in trials, appear to have little if anything to do with long term outcome. It is the long term outcome of needing a cane, wheelchair, bedridden status or death from MS that patients and their families and healthcare providers fear, not the one relapse every 2-5 years (which is the average) the number of which has no impact on their long term outcome. (See Appendix C– Scalfari et al.)

So in fact, relapses used to approve several drugs can be confidently discounted as important outcomes. In fact, relapses after year 2 are associated with better outcomes, making them without useful meaning as an outcome. Even worse, it took a long time before disability outcomes, (which had been discounted prior to the Jekyll Island referendum), were shown to be near worthless at least as measured in MS trials. (See appendix D. Ebers et al).

However the story behind these so-called “disability” measures is interesting on its own. SCHARR a pharmaco-economic unit in Sheffield was entrusted with doing the pharmaco-economic evaluation of Interferon and Copaxone prior to their use in the UK pending governmental approval. The risk-sharing scheme was a consequence in part. Finally someone with an objective (non-conflicted) approach had access to the primary data, given reluctantly by the companies. When SCHARR had a look at the raw data, they discovered that “disability” measures were not measuring anything of the sort. What they were measuring was the effects of the relapses, random variation and measurement error, and had no bearing on the development of long term disability. (See Appendix D Ebers et al).

When SCHARR brought these findings to light, within the bounds and governance of the Risk Sharing Scheme, administered by the MS Trust – a supposed “charity” run by a former Schering employee- legal action was threatened. This led to SCHARR being gagged by order as apparently this was in the terms of the contract. Apparently the terms of the Risk Sharing Scheme allowed for this.

Nevertheless the data came out in another way.

MRI OUTCOMES

MRI outcomes cannot be validated although newer methodologies may be better. See Appendix E (Goodin et al). In this paper we show that the change in MRI in the original Beta Interferon study (which was the basis of the drug approval) had no relationship to disability at 16 and 21 years. This should have been no surprise as Daumer et al (Appendix F) had shown the inter-centre variability for MRI measures was greater than the difference between treatment and placebo, and that MRI was a poor predictor of even short term outcomes like relapse rate.
THE SYLVIA LAWRY CENTRE

The Centre was established by private donation. The money from a private donor was given to the MSIF, Multiple Sclerosis International Foundation, to fund a data centre aimed at developing virtual placebos for comparisons. Having won the tender to develop such a centre, they successfully obtained placebo arm data from companies.

Regrettably, the governance of this centre was heavily dominated by industry-funded clinical triallists and MRI centres. Many had achieved prominence in the field largely by force of personality, naked aggression, and support from industry. There was obvious collusion among the members of this group and they had managed to put MS clinical trials research into a stranglehold from which it has not recovered. The financial gain for those centres was enormous (see Conflict of Interest).

The Sylvia Lawry Centre (SLC) collected the placebo arms of more than 40 trials. Industry was reluctant to donate the data but as two medical directors of MS therapy companies confided to me “What harm could the placebo arms do?”. It turned out quite a lot. When the placebo arms were evaluated, it became very clear that the measure of disability, indeed the one that the FDA used to approve Avonex for the prevention of disability was more or less meaningless! (see Ebers et al, appended)

An indication of the ethos of this field is the fact that the response from industry-funded investigators to these data, (remember these are the same data that were used to approve the drugs in the first place), has been to discredit the centre, withdraw its funding from the International Federation of MD Societies (30% of whose funding comes from industry and whose scientific board is dominated by those with major industrial conflicts of interest), and to attempt to discredit its supporters. The outcomes invalidated by SLC are still used and have been a basis for approval of many drugs such as fingolomid. The field has pretended these results don’t exist. The regulatory agencies have not reacted.

It has been discouraging all in all to discover how little support there has been for investigators who simply want to do the right thing. Additional sources of support, granting agencies, journals, academic colleagues and regulatory has been very largely neutralised by concerted action on the part of industry and their funded investigators.

In many cases, the errors made by regulatory agencies had been through simple naivete. So in the case of the Interferon data in the early ‘90s, the FDA mistakenly assumed that the influence of neutralising antibodies was nothing to worry about, because the relapse rate had not changed prior to and subsequent to the emergence of positive antibodies. What they failed to realise was in fact
that the relapse rate *should have gone down* because this is the natural history of the untreated disease. The fact that it stayed the same was a measure of the fact that antibodies were abrogating the effect on the outcome measures they highly valued.

They also made the mistake of listening to experts in the field who testified in front of the FDA that “MRI is the disease”. It seemed not to matter to them that those who were testifying were heavily funded by industry already, a level of funding which skyrocketed after approval and as it turns out, they were very much in error.

In addition, the FDA has asked the first Interferon approval company to collect long term data because after all it was approved on the basis of the MRI results not on the basis of clinical results which were meagre. However they did not enforce it. It took me several years to set up long term follow up on the original patients as there has been no systematic follow up.

So much in the same way as the euphonious declarations about data being in the hands of investigators, supposedly mandated by the journals held no substance, once again the regulatory agencies have let the patients and the field down by failing to enforce their own dictums. Perhaps this has resulted from extreme pressure from legislators.

**CONFLICTS OF INTEREST**

Conflicts of interest in the field have been ubiquitous. So in the case of MRI for example, a large MRI Centre prominent in MS trials has been said to have received nearly £20,000,000 (according to 2 credible industry sources) over the last decade or so - for monitoring MS clinical trials. Even if it is £10m this is plenty to influence interest. These are contracts struck with industry in which the nature of the transaction has to be considered a sham contract. This is a term popularised perhaps during the Siemens Inquiry (see the Wall Street Journal under the by-line of Crawford). So for many years drug companies had slid money to investigators in indirect ways. Accountants did not like anything that could be perceived or identified as a pay-off. So companies and investigators came up with the clever idea of executing sham contracts. What happens here is that a service is provided, there is a contract, it all appears in the balance sheets of both parties, the auditors and accountants are happy, but the key flaw is that the service is not worth anything near what is being paid for it. How the investigators came to this is variable. For some, they truly believed MRI was an important surrogate. For others who had tried and failed to validate MRI, motives may have been financial.

Illustrative of this shady procedure (sham contracts) – which might be illegal – are the contracts for MRI monitoring in MS clinical trials. Medical directors of two large pharmaceutical companies active in MS have told me that (paraphrased), “I know MRI is a lousy measure but this is an
effective way of putting money into the hands of the opinion leaders”. In the case of the situation at the large centre mentioned above, things are particularly disturbing since the scanner that was used for all this clinical trial monitoring was purchased for them by a charity – an MS society. This essentially meant that because the charity seems to have paid for the scanner, for technicians, and for maintenance and repairs, the institution had almost nothing but profit from the contracts. This was not explicitly stated to the charity and the charity had been kept in the dark. Lead investigator having profited greatly from this operation is the scientific chairman of the research advisory committee for the Multiple Sclerosis International Federation. He has been in this post for many years. I do not believe he has a term. He played a primary role in withdrawing the funding of the Sylvia Lawry Centre. He engineered the review which included one reviewer who had virtually no independent publications, therefore was highly inappropriate, and this reviewer was extremely aggressive and negative during the review which I attended and still has no MS publications.

So now the lead investigators on several clinical trials published in the New England Journal of Medicine and the Lancet do acknowledge their conflicts of interest with industry at the back of their papers but the extent of these conflicts is not spelled out and for some of them they are massive. The universities and institutions and their departments benefit from pay-outs from industry and many are heavily dependent upon them.

At individual investigator levels, the per capita costing for enrolling patients in trials is substantial, particularly in Eastern Europe where economies are weaker. Individual neurologist-investigators have enrolled as many as 100 patients or more in brief MS trials, generating incomes in one or two trials which they could not possibly make in 20 years by honestly looking after the sick.

Clearly the outcomes that have been used for 25 years now are more or less worthless as predictors of the long term outcomes that really matter to patients, families and third party payers. Yes, there is a weak association of these with baseline MRI but baseline only and none of the primary outcomes widely in use within trials can be validated against long term disability. Certainly the change in MRI over the course of the studies which have been published, has no independent contribution to long term outcome. Several data sets have not been published because the company does not like the results but. I have seen some of the data myself.

WHAT TO DO?

I suggest there should be an in-depth investigation and a two-day meeting on outcomes where a lot of the unwashed linen can be aired out and the depth of the conflict of interest of investigations considered. There needs to be a public airing of what has happened in MS. It is not unique but the
MS story speaks volumes about academics, universities, regulatory agencies and industry and their current ethos and relationships.

It is clear that the target of therapy in MS ought to be slowing or stopping the development of the progressive course of the disease because this is by far the biggest determinant of long term outcome. No study has attempted this. Industry funded investigators widely state that it would be impossible to do such a study but this is very largely self-serving. Changing the outcomes required must come from the regulators as it will not come from the academics who are hopelessly conflicted in this field.

Certainly patients can be found who are prepared to go for 4 years and forego other activities which would be incompatible with clinical trials. Moreover if progression were the primary outcome it is possible to select patients for likelihood of progression.

Regulatory agencies are the only ones now who can rescue what has become for me an intolerable situation. After 20 years of trying to apply a brake to the inexorable desertion of fundamental scientific and academic principles I have chosen to retire and do something else. However, all I can say is that if someone had told me this is what it would come to, I would not have thought it possible.

I have just come back from 2 meetings at which the notion of placebo treatment has been deemed "unethical". "Unethical" by the same investigators who are major recipients of industry cash, who have never seen the raw data in papers their names are on, who tell patients that medications will prevent disability and prevent progression when they know that there is no evidence this is true and who have no compunction in enrolling patients in trials where the outcomes have never been validated. There have been several deaths in MS trials and if these trials were using outcomes that have little meaning to patients what more needs to be said? Things have to change.

APPENDICES WHICH WILL BE EMAILED ALONGSIDE THIS SUBMISSION:


### 2. Specific comments on text

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<thead>
<tr>
<th>Line number(s) of the relevant text (e.g. Lines 20-23)</th>
<th>Stakeholder number (To be completed by the Agency)</th>
<th>Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using ‘track changes’)</th>
<th>Outcome (To be completed by the Agency)</th>
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