

**In-Depth Analysis of the “Summary Report -
CIHR and MS Society of Canada Joint
Invitational Meeting on Multiple Sclerosis
Research**

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Executive Summary

A detailed analysis of the recently released CIHR/MSSOC Report on CCSVI and Multiple Sclerosis (Beaudet Report) has found that the report contains many scientific errors and unsupported opinions. The serious scientific failings which permeate the Beaudet Report are painstakingly documented in over nine pages of text in the In-Depth Analysis.

An even larger and more serious problem with the Beaudet Report are the overt and most disconcerting ethical breeches. These ethical breeches include:

1. The committee organizers used an incredibly biased committee member selection process such that that no scientists or practitioners with expertise, knowledge and/or experience with CCSVI and MS were allowed on the Beaudet Committee
2. The majority of the Committee members (13/23) have an obvious conflict of interest when it comes to evaluating the need for a clinical trial to test the efficacy of a non-drug therapy for MS such as CCSVI treatment. Such a conflict of interest takes the form of close ties, often financial, with the pharmaceutical companies that manufacture and market the drugs that are currently used for MS. Such ties are meticulously documented in the Appendix of the In-Depth Analysis.
3. The conflicts of interest were not declared or even alluded to in the Beaudet Report
4. The committee members with a conflict of interest did not recuse themselves when it became obvious that CCSVI and the question of a CCSVI treatment clinical trial were going to dominate the discussions by the Committee. In fact, the compromised individuals strongly influenced the final recommendations of the committee.

The highly flawed science, in combination with the serious ethical breeches of the Beaudet Report, completely invalidates its recommendations. Given the above the Federal Health Ministry needs to:

1. Convene a new expert committee to examine and make recommendations on the need for a clinical trial to test the efficacy of CCSVI treatment for MS. The committee should be populated by both scientists and practitioners with expertise and experience with CCSVI and MS and scientists with experience in related topics such as venous angioplasty in other conditions, the neurovascular system, neuro-imaging and MS disease pathogenesis. Every effort should be made to exclude individuals with a clear conflict of interest related to past and/or present relationships with the pharmaceutical industry.
2. Launch an investigation into the ethical breeches of the Beaudet Report and determine how such a scientifically inappropriate and ethically challenged committee came into existence in the first place.
3. Review the appropriateness of having Alain Beaudet lead the Canadian Institutes of Health Research. Canadians need to have confidence in their health leaders and Beaudet's credibility has been destroyed by the scientific failings and the ethical breeches of the committee he formed and the report he wrote on a most important health issue.

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Introduction

On August 26th, the Canadian Institutes of Health Research (CIHR) and the Multiple Sclerosis Society of Canada (MSSOC) convened a meeting of a group of scientists from various disciplines “*to review evidence, current international efforts, and knowledge gaps related to the etiology and treatment of MS, with a special emphasis on neurovascular issues including the recently proposed condition called chronic cerebrospinal venous insufficiency (CCSVI)*”. The chair of the committee was Dr Alain Beaudet, the current president of CIHR and the report is herein referred to as the Beaudet Report. It can be accessed at (<http://www.cihr-irsc.gc.ca/e/42381.html>). Because of the great importance of CCSVI research, Direct-MS, Canada’s second largest MS charity, undertook an In-Depth Analysis of the Beaudet Report to determine if the Report was scientifically acceptable and free of ethical breaches.

The committee assembled by Dr Beaudet, with help from officials from the MS Society of Canada, consisted of five CIHR executives, including Dr Beaudet, three executives from MSSOC, ten clinical/research MS neurologists, two neuro-imaging specialists, one neurosurgeon, one vascular surgeon and one interventional radiologist. Notably, not a single committee member had any previous experience in any aspect of CCSVI research or treatment although two of the neurologists will be leading small studies on MS and CCSVI over the next two years. Notably, only two of the twenty three committee members brought critical expertise in extra-cranial vascular practice and research to the table.

The only scientific topic discussed by the Beaudet Committee was CCSVI and its relationship to MS and the only recommendations that were made related to future research directions for CCSVI and MS. There apparently was no discussion on other important topics such as “*current international efforts and knowledge gaps related to the etiology and treatment of MS*” and there are no recommendations regarding any MS research topic except CCSVI. This is most surprising given that Dr Beaudet had earlier testified before the Parliamentary Subcommittee on Neurological Diseases in June that “*This meeting is to be held in August and will focus on how best to accelerate research and innovation in MS.... The expected outcome will be a richer understanding of clinical research priorities regarding potential innovations related to diagnosis and treatment of MS.*” There is no resemblance whatsoever between what Dr Beaudet had promised Parliament and what actually was delivered by the Beaudet Report.

Given that the meeting was dedicated to a discussion of CCSVI, it is clear from the content of the Beaudet Report that the participants did not have adequate knowledge of:

- 1) the origin, manifestation and detection of CCSVI,
- 2) the CCSVI literature,
- 3) the substantial international effort which is currently going on regarding CCSVI treatment.

When one considers the committee members' lack of any expertise and experience with CCSVI and MS, this is exactly what one would have expected. Although the failure of the committee members to properly collect and analyze the available data on CCSVI is predictable and understandable, such a failure is unacceptable and it unequivocally negates the validity of the recommendations of the Beaudet Report.

Another major problem with the Beaudet Report is that a review of the committee members' past research and/or executive activities has revealed that many have an overt conflict of interest in the regards to the potential introduction of an effective, non-drug therapy, such as CCSVI treatment, for MS. Such a potential ethical problem calls into question the objectivity of the discussions and the resulting recommendations of the Beaudet Report and provides another reason why the recommendations cannot be taken seriously.

In summary, if an important scientific issue needs discussion so as to generate recommendations to help guide government policy, it is absolutely imperative that those involved have:

- considerable expertise, knowledge, and experience in the topic at hand,
- that all sides of the topic are adequately discussed,
- that no one involved has a conflict of interest.

The Beaudet Committee fails on all three counts in that not a single participant has any expertise or experience with CCSVI, nothing positive about CCSVI was discussed, and not one, but many, participants have clear conflicts of interest.

Finally, given the importance of CCSVI research to Canadians, there is no doubt that a government-led investigation is required to determine how such a scientifically inappropriate and ethically challenged committee came into existence in the first place. Canadians, especially those with MS, deserve better than this.

Scientific Failings of the Beaudet Report

The scientific failings in the Beaudet Report range from relatively minor errors of fact to very large errors of interpretation of the relationship between CCSVI and MS. Another failing is the absence of key references and this problem is

magnified by the fact that there are not many references available in the first place. Perhaps the biggest problem of the report is the complete failure to acknowledge what is happening regards to CCSVI treatment worldwide.

In the discussion of Dr Zamboni's clinical research, the report conveys the false impression that Dr Zamboni tried to claim that CCSVI was the only cause of MS and that anyone with CCSVI will also have MS. Dr Zamboni has never made such claims and he simply drew attention to the fact that a high proportion of people with MS may well have impaired venous drainage and that such a problem could well be part of the MS disease process. Thus statements in the report which try to discredit the CCSVI hypothesis by claiming that "*patients who develop blood clots in these veins, or who have these veins removed during head and neck cancer surgery, do not develop MS*" are completely inappropriate and valueless and show a lack of understanding of Dr Zamboni's work. No one involved in CCSVI research is claiming everyone with CCSVI has or will develop MS and it is well recognized and accepted that genetic and environmental factors besides CCSVI are important factors in MS etiology and pathogenesis.

The report also tries to discredit Dr Zamboni's clinical research (Zamboni et al, 2009a) by claiming it was not a controlled, randomized, double-blind trial. Once again, given that the Zamboni clinical trial was simply a pilot trial, and the first of its kind, it is entirely inappropriate to criticize it for not being controlled, randomized and double-blinded. **No pilot trials have such rigour.** Dr Zamboni's pilot research, like all pilot trials, was done to demonstrate the safety of the procedure and to determine if any improvements occurred in treated patients. Notably, both safety and possible efficacy were shown. Finally, Dr Zamboni concluded that the results of his pilot trial indicated that more rigorous clinical research was required.

In summary, the criticisms of the Zamboni work in the Beaudet Report have no substance and are inappropriate. No one is claiming Dr Zamboni's initial trial is anything more than a pilot study. However, as such, **its results more than justify the need for more rigorous clinical treatment research.**

The most serious scientific flaws in the Beaudet Report are found in the two sections entitled "*Is there such a condition as "chronic cerebrospinal venous insufficiency, or CCSVI?"*" and "*Is "venous insufficiency" linked to MS?"*" There is no doubt that both of these questions are valid and critical questions to examine when it comes to determining the need for further clinical research into the effectiveness of CCSVI treatment. The problems with the Beaudet Report lie not with the questions themselves, but with how the questions are answered.

In the first section, *Is there such a condition as "chronic cerebrospinal venous insufficiency, or CCSVI?",* the report points out that venous drainage of the brain is a highly flexible system. This is well accepted and is the reason why CSSVI is not an acute problem but rather is a subtle, chronic one associated with delayed

drainage times and hypoperfusion. This creates problems over decades rather than days. The report completely misses this key aspect of CCSVI.

In this section, it is stated that “*A proportion of the brain’s venous drainage runs through the Internal Jugular Veins when standing, however when lying down, that proportion of the venous return tends to flow through alternate venous routes.*”

Such a statement is completely erroneous and exactly the opposite is true.

The jugular veins are important drainage paths in the supine position and are often collapsed when one is in the standing position. Such a fundamental error reflects the inexplicable and inexcusable, near absence of extra-cranial vascular expertise on the Beaudet Committee.

All other statements in this section are either irrelevant or inappropriate to the question at hand. The final statement in this section that “*there is little support for the notion that venous insufficiency for the brain or spinal cord contributes to the development of MS*” is a completely unsupported opinion which telegraphs the strong negative bias of the Beaudet Committee.

In the section “*Is “venous insufficiency” linked to MS?*”, the report has missed a number of very important references, has emphasized a few, scientifically questionable, negative studies and has completely ignored what is happening in numerous CCSVI clinics throughout the world. The question of association of CCSVI and MS is an important one and must be established before clinical treatment research would be deemed necessary.

The Zamboni research (Zamboni et al 2009b) found a greater than 95% association of CCSVI with MS although less than 200 patients were tested. Most importantly, the results were checked and corroborated with selective venography, the accepted gold standard for the determination of CCSVI, and thus can be considered to be reliable. On the other hand, any scientific studies which do not include venography to corroborate the determination of CCSVI can be considered highly suspect and have to be given little weight. The reason for this is that non-invasive techniques such as Doppler and MRV have a very high rate of false negatives and can be highly operator dependent.

The subsequent University of Buffalo work demonstrated an almost 3X higher prevalence of CCSVI in persons with MS in a large study of 500 people (University of Buffalo, 2010). Notably, the person doing the determination of whether or not CCSVI was present with a Doppler technology was properly trained and had months of experience. Furthermore, the reliability of the Doppler results was checked with venography (Hojnacki et al, 2010).

It was very surprising that the Beaudet Report did not refer to other published studies of CCSVI/MS association which include Al-Omari and Rousan (2010) which found 84% of persons with MS had CCSVI (sample size 25) and no healthy controls had CCSVI (sample size 25) and Simka et al (2010) which found CCSVI in 90% of persons with MS (70 sample size). Notably, both these results

were based on selective venography which leaves no doubt as to the accuracy of these data.

It is also worth noting that Dr Simka updated his findings at the June Parliamentary Subcommittee meeting which was attended by Dr Beaudet. At that time Dr Simka reported “*total number of people who have been treated is now about 400. CCSVI has been found to highly correlate with multiple sclerosis. Only 3% of the multiple sclerosis patients we have seen were not diagnosed with CCSVI, using colour Doppler sonography, magnetic resonance venography, and standard venography.*” Given there are not a large number of references on CCSVI and MS, the omission of these key references, which are readily found on Pubmed, shows a definite lack of familiarity of the Beaudet Committee with the CCSVI literature.

The Beaudet Report, in keeping with its very negative bias, emphasized two small negative studies (Doepp et al, 2010; Krogias et al, 2010) which reported finding essentially no CCSVI associated with MS. Notably, both studies used only operator-dependent, non-invasive techniques and did not use any selective venography. Thus the results are very unreliable and contribute very little to the question of MS/CCSVI association. The Beaudet Report neglected to mention the critical lack of selective venography for the negative studies.

Perhaps one of the most important pieces of evidence regarding the association of MS and CCSVI is the fact that over 100 persons with MS are being treated for CCSVI every day (2000 a month) and well over 5000 persons with MS have already been treated for CCSVI worldwide. Notably, the daily number of CCSVI treatments is increasing every week as more and more clinics open up, especially in the USA. Clearly, if CCSVI was not associated with MS, there would not be such a booming and ever expanding medical practice of treating persons with MS for CCSVI. If CCSVI was not highly associated with MS, the treatment of CCSVI in MS patients would never have gotten off the ground. By ignoring this major phenomenon, as well as various key references, the Beaudet Committee loses all credibility when it comes to the analysis of the association of CCSVI with MS.

The last line in this section “*These recent studies have demonstrated a wide variation in the patterns of venous drainage of the brain in both MS patients and people with no evidence of MS (controls), underlining the difficulty involved in concluding that a vein that is ‘narrowed or blocked’ will cause MS.*” applies only to studies which use non-invasive, detection techniques and reveals a lack of familiarity of the Beaudet committee members with how CCSVI is best detected. **All studies which have used selective venography, the only reliable method for determining the presence or absence of CCSVI, have found a high association of CCSVI with MS.**

The next question that the Beaudet Report asks is “*Does venous angioplasty work?*”. The report claims that “*Venous angioplasty is rarely used because the*

incidence of re-stenosis is so high.” However, given the obvious dearth of venous angioplasty expertise on the Beaudet Committee, such an unreferenced statement has to be questioned. In contrast to this statement, Dr Robert Maggisano, a vascular surgeon with 30 years experience, testified before the June Parliamentary Subcommittee that *“We treat veins and arteries with angioplasty routinely”*. Furthermore, in a recent position statement of the Society of Interventional Radiologists, it was stated that *“balloon angioplasty and stent placement of central thoracic veins have been performed safely for many years in other clinical scenarios”* (Vedantham et al, 2010).

In summary, there is no doubt that venous angioplasty works because it has been used for many years and is in use today. If it didn't work, such a procedure would have been abandoned years ago. The fact that it is currently being used for CCSVI treatment in many clinics around the world, including the prestigious Arizona Heart Institute, shows that many interventional radiologists and their review boards are satisfied that it works. A claim that it doesn't work by a committee dominated by neurologists and executives cannot be taken seriously, especially given the unrelenting negativity which pervades the report.

The final question of the report *“Is the venous angioplasty treatment safe and efficacious?”* is really two questions, one on safety and one on efficacy. Both are important and both need proper, well supported answers. By combining them, the Beaudet Report does not answer each separately and this is very misleading. For example the report states *“In order to evaluate whether any treatment is efficacious and safe, it is essential to compare the treatment in a blinded fashion to a control MS population that does not receive the treatment.”* This statement is both erroneous and correct. This statement is completely wrong in terms of determining safety but is basically right in terms of determining efficacy.

So let's look at the question of safety first and the answer to this is paramount for any recommendation of whether clinical trial research should be funded at this time. Overall, the evidence shows that venous angioplasty is very safe and this is emphasized by Dr Maggisano in his testimony *“We treat veins and arteries with angioplasty routinely. It has a low-risk and a very minimally invasive component to it. Most of these treatments are outpatient treatments.”* Dr Simka in his testimony stated that *“The group of 347 CCSVI patients with associated multiple sclerosis have undergone a total of over 500 endovascular procedures, including 414 balloon angioplasties and 173 stent implantations. In this group, there were only a few rather minor and occasional complications or technical problems related to the procedures.”* These data are now in a scientific paper (Ludyga et al, in press) and the failure of the Beaudet Committee to consult Dr Simka on the safety issue when they knew he had a large and reliable data base on the issue reveals a lack of initiative in obtaining important data on a key question.

In summary, there is no question, based on published work and long years of experience with venous angioplasty, that such a procedure is very safe. As Dr Beaudet testified in June, *“I know of no procedure, even eating natural food, that*

is 100% safe.” However, the data and long years of experience indicate that venous angioplasty is about as safe as any medical procedure can be.

In terms of the question of the efficacy of venous angioplasty for MS, the Beaudet Report went back to bemoaning the lack of rigour of the Zamboni pilot trial and that the results can not be taken as proof of efficacy. Everyone agrees with this but that is not the point. There is no doubt we do not know if venous angioplasty is effective for relieving symptoms and/or slowing disease progression. Only a proper clinical trial will determine this. The Beaudet Report presents a Catch 22 in that they cannot recommend funding a proper clinical CCSVI treatment trial until we know it works. The absurdity of such logic needs no further elaboration.

The last line in this section contains two unsupported and completely erroneous pronouncements. The first one claims that “*there is currently no scientifically valid evidence in support of the existence of CCSVI in patients with MS*” As has been demonstrated, there is a very large and robust published data base that CCSVI is undoubtedly associated with MS and the thousands of CCSVI treatment procedures that have already been done and the over 100 CCSVI treatment procedures being done every day only reinforce this inescapable conclusion. Any claim to the contrary essentially says that fraudulent interventional radiologists are practicing in the many areas throughout the world, including the Arizona Heart Institute, which in the past has treated presidents of the United States.

The second unsupported and baseless pronouncement is that “*there is currently no scientifically valid evidence to support the use of venous angioplasty in the treatment of patients with MS*”. As has been discussed, venous angioplasty is an extremely safe procedure. Secondly, a pilot trial has indicated that the procedure may well be of value for MS. Furthermore, the fact that the treatment is already in use in many countries of the world suggests that the review boards of the clinics doing such procedures are satisfied there is sufficient scientific evidence to support the use of venous angioplasty for MS. Finally, it can be argued that the many hundreds of well documented accounts of improvements following venous angioplasty represent valid scientific observations. In his testimony Dr Simka noted that “***But what I can say now about what we are seeing after one or two months of the treatment is that about 80%, 90%, of the patients experience improvement***”. Although such information is usually ignored as being simply “anecdotal”, it is based on unbiased observation and should be given some weight.

In summary, there is overwhelming evidence that CCSVI is strongly associated with MS and there is ample scientific evidence and logical arguments to support the need for a clinical trial which tests the efficacy of venous angioplasty for MS. In fact, it is only common sense to agree with the sentiments of both Dr Zamboni who told the June Parliamentary Subcommittee “*I think it is irresponsible not to proceed with angioplasty treatment of CCSVI in patients with multiple sclerosis under the umbrella of controlled studies, supervised by ethical committees in*

tertiary hospitals, and with all the capability in interventional radiology and in vascular and endovascular surgery.”, and Dr Maggisano who passionately stated “So I would really urge the committee members, the government, and the appropriate funding agencies to look towards funding the definitive study that will answer the question, does treatment of the venous outflow obstruction improve the neurological outcome?”

There can be no doubt that we need to find out as soon as possible if venous angioplasty is an effective treatment for MS. It has been stated that “Time is Brain” when it comes to MS and, every year that the necessary treatment research is delayed, tens of thousands of Canadians may well be suffering the unnecessary loss of neurons and associated functions.

The Beudet Report finishes with a *Summary* section and a *Recommendations* section. Each summary point and each recommendation is discussed below.

Summary Point 1 - To date, the published evidence that venous abnormalities (i.e., CCSVI) play a role in the cause or propagation of MS is contradictory and, as such, should be treated with circumspection. This is a subject that needs prompt further study. To address this pressing need, the MS Societies of Canada and the US have funded seven studies to further determine if patients with MS have venous abnormalities that differ from age matched controls.

This summary point is very misleading because the seven studies funded by MSSOC and NMSS will NOT address the question of whether or not CCSVI is a causal factor in MS. They will simply address the question of MS/CCSVI association, a question which has already been positively and unequivocally answered by reliable, venography-based studies and the thousands of patients who have already been treated. Notably these seven studies may well not produce reliable results because they will only be using non-invasive imaging techniques for CCSVI detection. The lack of venography will substantially downgrade the results.

The question of CCSVI as a causal factor in MS was never addressed in the Beudet Report. To answer such a question it is necessary to fulfill the key criteria of Hill (1965) for an associated factor being a causal factor. Given that:

- 1) CCSVI is highly associated with MS.
- 2) The venous malformations which cause CCSVI are congenital and thus precede the MS disease process (Lee et al, 2009; Lee et al, 2010).
- 3) Biologically plausible mechanisms related to CCSVI (iron deposition, hypoperfusion, upregulation of endothelial adhesion molecules) can be readily related to the MS disease process

It is reasonable to interpret that CCSVI is indeed a causal factor for MS because it fulfils the three key criteria of Hill (1965). Of course this makes the initiation of a clinical treatment trial even more urgent.

Summary Point 2 - *Seven North American studies (\$2.4 million in funding by the MS Societies of Canada and USA) will carefully evaluate whether CCSVI occurs. The studies will define mechanisms of how venous drainage from the brain might be of relevance to MS, an issue that has not yet been adequately explored.*

As noted above, these studies will simply add to the already overwhelming evidence that CCSVI is associated with MS. They will NOT define mechanisms of how venous drainage from the brain might be of relevance to MS.

Summary Point 3 - *In the absence of clear and convincing evidence for CCSVI, the performance of an interventional venous angioplasty trial with its attendant risk to MS patients is not appropriate at this time. It is unlikely that a proposal based on the current procedure of Doppler assessment of venous narrowing and subsequent venoplasty would pass a peer review panel (the international standard of scientific excellence and the standard for much of the funding in Canada), because evidence that CCSVI exists is currently lacking. Similarly, there are serious ethical issues associated with doing such a trial given the lack of convincing evidence for CCSVI.*

There is no doubt that we have *clear and convincing evidence for CCSVI* if only on the basis of the 5000 venograms of MS patients who have been treated. However, there are numerous published scientific papers that clearly illustrate the presence and reality of CCSVI and it has been accepted as a recognized pathological condition by the International Union of Phebiologists (Lee et al, 2009).

The performance of an interventional venous angioplasty trial is critically needed at this time because:

- CCSVI is definitely highly associated with MS,
- CCSVI is very likely a causal factor of MS
- A pilot trial established the safety of venous angioplasty for MS and indicated in may well have efficacy.
- Many hundreds of well documented experiential accounts of substantial improvement following venous angioplasty have been made available on TV, in newspapers and on the Internet.
- Thousands of Canadians will be traveling out of Canada to seek CCSVI treatment in the future and it is imperative for them to make an informed decision on whether or not to do this. Only a proper clinical treatment trial will provide the required information for such a decision.
- *It is unethical for us to withhold a simple, safe, and relatively inexpensive treatment from people who are facing a devastating medical condition especially when these people may, as a consequence, assume an even greater personal and financial risk by pursuing treatment by providers of uncertain ability, in remote locations, and who do not provide follow up care (Andrews, 2010).*

There is no doubt that a properly planned CCSVI treatment trial would pass an objective review committee. Notably, CCSVI treatment has been approved at numerous hospitals in the USA and they would use the same criteria for approval as any review committee in Canada.

There are NO ethical issues associated with doing such a trial just as there are no ethical issues for the many hospital review boards in the USA that have approved CCSVI treatment. The only ethical issues associated with CCSVI are associated with the question of why the neurological community, which has very large and complex financial ties to the pharmaceutical industry, is working so hard to prevent a most needed trial of a non-drug therapy from happening.

Summary Point 4 - If a clinical treatment trial for CCSVI in MS were to be considered, one cannot expect a quick outcome given the natural course of the disease. Indeed a meaningful clinical trial could be as long as several years, with regular and repeated post-operative measurements of the key symptoms of the disease, which would add greatly to the expense of the trial. A trial of CCSVI for symptoms of MS such as fatigue or weakness would have to be compared to other available symptomatic MS therapies.

Everyone agrees that a proper trial would likely take 2 years just as drug trials do. The cost is yet unknown but cost cannot be used as an argument against the clear need for such a trial. The appropriate funding can be found across Canada because the outcome of the trial will be felt countrywide.

One aspect of cost/benefit that is rarely stated is, that if CCSVI treatment is proven to be effective, it may well replace the need for expensive drug therapy for many. In this situation, there would be billions of dollars saved by provincial health departments in the future. Of course, the potential loss of such major drug revenues is of considerable concern to those that have substantial financial ties to the pharmaceutical companies that manufacture and market the current MS drugs.

Recommendation 1 - Effective immediately, to establish a scientific expert working group made up of the principal investigators of the seven MS Society-sponsored studies (four from Canada and three from the US), scientific leadership from CIHR and the MS Societies, and a representative from the provinces and territories, to monitor and analyze preliminary and final results from these studies, as well as from other related studies from around the world related to venous anatomy and MS. The first meeting of this expert working group should take place in this calendar year.

Such a scientific working group is not needed now or in the future, especially one that would be populated by persons who have an obvious conflict of interest. The principal investigators of the seven studies and the scientific leadership from MS societies all have financial ties to pharmaceutical companies. Furthermore, the results of these studies will add very little to what is already known about the CCSVI/MS relationship. The existence of such a group would be a waste of time and money.

Recommendation 2 - Based on the outcomes of these studies, the scientific expert working group should reach conclusions regarding (1) a common standard for reliably diagnosing the proposed CCSVI condition using imaging or other techniques, and (2) clarity regarding a potential association between impaired cerebral venous drainage and MS.

It is already well established that selective venography is the gold standard for determining the nature and the location of the venous anomalies which cause CCSVI. In almost all cases, the seven studies funded by MSSOC and NMSS do NOT include venography and thus their results will be unreliable because of the lack of corroboration with venography. They will definitely NOT help to establish a common standard for reliably diagnosing the proposed CCSVI condition using imaging or other techniques.

There is already absolute clarity regarding the high association of CCSVI with MS. As noted above, the lack of use of selective venography in the seven studies will ensure that they add nothing to the already answered question of CCSVI/MS association. If the researchers want to verify the MS/CCSVI association for themselves, they can readily spend a week at a CCSVI treatment centre (e.g. Arizona Heart Institute) and watch the selective venography of all the treated patients. Such first hand experience should leave no doubt in their minds.

Recommendation 3 - Depending on these conclusions, the scientific expert working group is to make recommendations on further studies including, if appropriate, a pan-Canadian interventional clinical trial that would evaluate the safety and efficacy of venous angioplasty in patients with MS.

The proposed scientific working group, made up mainly of persons with conflicts of interest when it comes to testing a non-drug therapy for MS, is the last group of people anyone would want to consult for a fair and objective evaluation of the need for a CCSVI treatment trial. This would be like asking oil company executives if we need a definitive study on climate change. Furthermore, it is very likely the results of the seven studies will be all over the map because they are using only non-invasive testing procedures which are known to not reliably detect CCSVI in many cases. The fact that the researchers are not using venography shows a lack of understanding of CCSVI detection or possibly a desire to fail.

The current data which are available and which have been discussed herein are by far enough to justify the need for a proper CCSVI treatment trial in Canada which has the highest rate of MS in the world. Dr Maggisano said it best when he testified in June that **“we need to get going on this, so that within a year or two we can let our MS population know the answer.”** Anyone who disagrees with such a common sense, objective conclusion would seemingly lack compassion for persons with MS and may well have a conflict of interest.

Ethical Problems Associated with the Beaudet Report

All the serious scientific flaws of the Beaudet report which are documented above are certainly very disconcerting and they essentially destroy its credibility.

However, **just as disconcerting are the ethical problems that are associated with the Beaudet Committee/ Report.** The first red flag, when it comes to the lack of ethics of the Beaudet Committee, is the fact that the committee did not include any scientists who had expertise and experience in CCSVI. This major problem has been recently elaborated upon by Dr Lorne Brandes in an open letter to the Federal Minister of Health (<http://healthblog.ctv.ca/post/An-open-letter-to-the-federal-health-minister-about-CCSVI.aspx>). As Dr Brandes notes “*the problem..is that, to the last individual, these experts represented just one side of this important and complex issue. As a result, the negative answer you received was certainly predictable.*” **There is no doubt that such a biased selection of committee members who were charged with advising the Minister of Health on a very important health issue represents a major ethical breach.**

The other major ethical issue that casts a dark shadow on the Beaudet Committee/Report is the fact that the majority of the committee members have a conflict of interest when it comes to evaluating the need for a clinical trial to test the efficacy of a non-drug therapy such as CCSVI treatment. Such a conflict of interest takes the form of close ties, often financial, with the pharmaceutical companies that manufacture and market the drugs that are currently used for MS. Because CCSVI treatment has the potential to replace the current drugs, resulting in a major loss of revenue for the pharmaceutical companies (\$10 billion in annual sales for MS drugs), anyone receiving financial benefits, including research grants, from the pharmaceutical companies would be in an obvious conflict of interest when it comes to deciding if a CCSVI clinical trial should go ahead. Clearly, it would be in their best financial interest if it did not.

As an example of such close relationships with pharmaceutical companies, Alain Beaudet appointed Dr. Bernard Prigent, vice-president of Pfizer Canada, to CIHR’s governing Council. Dr. Alain Beaudet, in the context of this appointment, emphasized the need to intensify collaboration and even to align CIHR’s “agenda” and “vision” with the pharmaceutical industry. Notably Pfizer markets the popular MS drug, Rebif.

The **thirteen** Beaudet Committee members with a readily identifiable conflict of interest include: Alain Beaudet, Anthony Traboulsee, Jack Antel, Wee Yong, Paul O’Connor, Jerry Wolinsky, Aaron Miller, Douglas Arnold, Brenda Banwell, Ruth Ann Marrie, Yves Savoie, Jon Temme, and Karen Lee. Some of the past relationships these people have had with drug companies are listed in Appendix 1. Notably, some of the remaining ten people on the committee also may be in conflict of interest but such conflicts are not as obvious and easily determined as those for the thirteen people listed above. The fact that no conflicts of interest were declared by the contributors to the discussions which formed the basis of the Beaudet Report can itself be considered an additional breach of ethics.

Clearly they should have recused themselves when it became obvious that CCSVI and the question of a CCSVI treatment clinical trial was going to dominate the discussions by the Committee.

There can be no doubt that the reliability of the Beaudet Report is completely compromised by the fact that the majority of contributors have a conflict of interest. These substantial ethical problems in combination with the major scientific flaws of the Report render the Report unfit for federal government consumption, especially when it comes to a major health issue such as the need for a CCSVI treatment trial.

Furthermore, the highly biased and negative nature of the Report is readily explained by the ethical issues surrounding it. In a more circuitous manner, the unacceptable scientific content can be related to the ethical issue of the biased selection of the committee members. It would be expected that a report on the science of CCSVI and MS by a committee that did not include anyone with a solid knowledge or experience of CCSVI and MS would be hopelessly flawed, as the Beaudet Report is.

Summary

Because the Beaudet Report on CCSVI and MS is scientifically flawed and is ethically challenged, the recommendations of the Report have to be put aside and not used to influence a decision on whether or not to fund a clinical treatment trial for CCSVI. The scientific discussions and arguments in the Report ignore many important data and interpretations and are highly biased. The report also contains clear scientific errors and most of the pronouncements are unsupported, biased opinions which are in disagreement with the current data.

The lack of a reliable and objective scientific analysis of CCSVI and MS in the Beaudet Report is due mainly to the biased selection of committee members that restricted participation to scientists having no expertise or experience with CCSVI and MS. Furthermore, most of the committee members, including the chair himself, have a conflict of interest, and such people should have been excluded from any decision making when it comes to recommendations regarding a CCSVI treatment trial. The fact that such compromised individuals strongly influenced the recommendations further negates the reliability and acceptability of the Report and its recommendations.

Health Canada needs to convene an objective committee to properly gather and analyze the current information on CCSVI and MS so as to provide a comprehensive and balanced report which includes reliable and well supported recommendations regarding future funding of CCSVI treatment research in Canada. The committee should be populated by both scientists and practitioners with expertise and experience with CCSVI and MS and scientists with experience in related topics such as venous angioplasty in other conditions,

the neurovascular system, neuro-imaging and MS disease pathogenesis. Every effort should be made to exclude individuals with a clear conflict of interest related to past and/or present relationships with the pharmaceutical industry.

Finally, Health Canada should seriously consider launching an investigation into the serious ethical breaches of the Beaudet Committee. Also the Government of Canada may want to reexamine the type of person they want leading their main health funding institution. The scientific and ethical failings of the Beaudet Committee are nothing short of shocking. The Committee's highly subjective and unsupportable recommendations are potentially very harmful to the many Canadians who have MS. This entire debacle provides everyone with some good lessons on how science can be perverted by ignorance and subjectivity so as to produce recommendations which potentially will serve a few professionals and harm many people afflicted with a very serious illness.

References

Andrews, T, Chronic Cerebrospinal Venous Insufficiency, Webcast presentation available at <http://www.youtube.com/watch?v=uAlbdW2aiYs>.

Al-Omari MH, Rousan LA, Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis, *Int Angiol.* 2010 Apr;29(2):115-20

Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ, No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol.* 2010 Aug;68(2):173-83.

Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.

Hojnacki D, Zamboni P, Lopez-Soriano A, Galleotti R, Menegatti E, Weinstock-Guttman B, Schirda C, Magnano C, Malagoni AM, Kennedy C, Bartolomei I, Salvi F, Zivadinov R. Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency: a pilot study in multiple sclerosis patients and healthy controls. *Int Angiol.* 2010, 29(2):127-39.

Krogias C, Schoder A, Wiendl H, Hohfeld R, Gold R, Chronische zerebrospinale venöse Insuffizienz“ und Multiple Sklerose. *Nervenarzt* 2010 April 81:740-746.

Lee BB, Bergan J, Gloviczki P, Laredo J, Loose DA, Mattassi R, et al. Diagnosis and treatment of venous malformations Consensus Document of the International Union of Phlebology (IUP)-2009. *Int Angiol.* 2009; 28: 434-51

Lee AB, Laredo J, Neville R, Embryological background of truncular venous malformation in the extracranial venous pathways as the cause of chronic cerebro spinal venous insufficiency. *Int Angiol.* 2010 Apr;29(2):95-108.

Ludyga, T, Kazibudzki, M, Simka, M, Hartel, M, Świerad, M, Piegza, J, Latacz, P, Sedlak, L, Tochowicz, M, Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? *Phlebology*, in press.

Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M, Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. *Int Angiol.* 2010 Apr;29(2):109-14.

University of Buffalo. First Blinded Study of Venous Insufficiency Prevalence in MS Shows Promising Results. Press release, February, 10, 2010. Available at <http://www.buffalo.edu/news/10937>

Vedantham S, Benenati JF, Kundu S, Black CM, Murphy KJ, Cardella JF. Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association. *J Vasc Interv Radiol*. 2010, 21(9):1335-7.

Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Giancesini S, Bartolomei I, Mascoli F, Salvi F., A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg*. 2009a, 50(6):1348-58.

Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009b;80:392-399.

Appendix 1 Ties to Pharmaceutical Companies by Members of the Beaudet Committee

Alain Beaudet - Dr. Beaudet appointed Dr. Bernard Prigent, vice-president of Pfizer Canada, to CIHR's governing Council—the first pharmaceutical representative to be so appointed. **Dr. Alain Beaudet in the context of this appointment, emphasized the need to intensify collaboration and even to align CIHR's "agenda" and "vision" with the pharmaceutical industry.** Notably Pfizer markets Rebif, one of the main MS drugs in use today.

It is also worth nothing that Pfizer has been a "habitual offender," persistently engaging in illegal and corrupt marketing practices, bribing physicians and suppressing adverse trial results. Since 2002 the company and its subsidiaries have been assessed \$3 billion in criminal convictions, civil penalties and jury awards. The \$2.3-billion settlement in September 2009 – a month before Dr. Prigent's appointment – set a new record for both criminal fines and total penalties.

Wee Yong – Yong has consulted for Teva Neuroscience, Serono, Berlex, Osprey Pharmaceuticals, Paratek, and Novartis and has also worked for Stem Cell Therapeutics Corp. As a consultant for Teva Pharmaceutical Industries, an Israeli company, Yong regularly packs his bags and heads off to explain to neurologists around North America exactly what those drugs do on a cellular level.

Paul O'Connor – O'Connor has received grants for clinical research from: Bayer HealthCare Pharmaceuticals; Biogen Idec Inc.; Merck Serono; sanofi-aventis and has served as an advisor or consultant for: Bayer HealthCare Pharmaceuticals; Biogen Idec Inc.; Merck Serono; Novartis Pharmaceuticals Corporation; sanofi-aventis; Teva Neuroscience, Inc.

Jack Antel - Antel reports having received honoraria (>\$10,000) from Novartis Pharmaceuticals Corporation.

Douglas Arnold - Dr. Arnold has received honoraria from serving on the scientific advisory boards of Biogen Idec and Genentech; holds a patent (Method of Evaluating the Efficacy of Drug on Brain Nerve Cells); has received speaking fees from Biogen Idec, Genentech, has served as a paid consultant for Biogen Idec, Eisai Medical Research Inc., Genentech, MS Forum, NeuroRx Research, Novartis, and Teva Neuroscience; and has received research support from Biogen Idec.

Brenda Banwell - Banwell has received Speaker's Honoraria from Biogen-Idec, Merck-Serono and Schering.

Jerry Wolinsky - Wolinsky has served on advisory boards or data monitoring committees, has had consulting agreements, or has received speaker honoraria from Acorda Therapeutics Inc., Acetilon Pharmaceuticals Ltd., Antisense Therapeutics Limited, Bayer Schering Pharma, Eli Lilly and Company, EMD Serono, Inc., Facet Biotech Corporation, Genentech, Inc., Novartis, Peptimmune, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., has received royalties for outlicensed monoclonal antibodies through the University of Texas Health Science Center at Houston

Aaron Miller - Miller has served on scientific advisory boards for sanofi-aventis, Biogen Idec, GlaxoSmithKline, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., Daiichi Sankyo, Merck Serono, Novartis, Ono Pharmaceutical Co. Ltd., and Acorda Therapeutics Inc.; has served on speakers' bureaus for and received speaker honoraria from Biogen Idec and EMD Serono, Inc.; has received funding for travel or speaker honoraria from sanofi-aventis, Biogen Idec, Daiichi Sankyo, Ono Pharmaceutical Co. Ltd., and Acorda Therapeutics Inc.; and receives research support from Acorda Therapeutics Inc., Teva Pharmaceutical Industries Ltd., Novartis, Genentech, Inc., Genzyme Corporation, and sanofi-aventis.

Ruth Ann Marie - Marrie has received research support from BioMS Medical, sanofi-aventis, Bayer Schering Pharma (Berlex), EMD Serono, Inc.,

Anthony Traboulsee - Traboulsee serves on a scientific advisory board for BioMS Medical; has received speaker honoraria from Bayer Schering Pharma, Teva Pharmaceutical Industries Ltd., and EMD Serono, Inc

Yves Savoie, Jon Temme, and Karen Lee – Savoie, Temme and Lee, are high ranking executives of the MS Society of Canada. The Society receives substantial grants every year from the pharmaceutical companies which manufacture drugs for MS. Furthermore, the pharmaceutical companies also help to sponsor individual events for local chapters across Canada.