

**Key Principles for Protecting the Integrity of the  
Canadian Data Safety and Effectiveness Network (DSEN)**

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The Canadian federal government's financial commitment (\$32 million over the first 5 years and \$10 million per year thereafter) to a national Data Safety and Effectiveness Network (DSEN) <1>, and the first call for applications by the DSEN for post-marketing studies are positive developments for consumer and patient safety. Hosted by the CIHR, the DSEN will conduct scientifically rigorous "real world" studies on the safety and effectiveness of post-market drugs in Canada (i.e., drugs already available) and will build the capacity to do so. The DSEN is a virtual network of Canadian centres of excellence in post-marketing pharmaceutical research that will have a common research agenda and strategic direction set by a DSEN Oversight Committee. There has been surprisingly little research in the public domain on the long-term safety and effectiveness of drugs once they have been approved and used by Canadians, although this information is needed by drug regulators, policy-makers, health care providers, and consumers.

We believe it is essential for the DSEN to secure the public's confidence quickly. There have been urgent calls for better adverse event reporting and better designed studies <2,3> in the wake of several controversies <4,5>. The most notorious of these controversies is undoubtedly the one that resulted in the withdrawal of Rofecoxib (Vioxx), where "there may be tens of thousands of patients who have had major adverse events attributable to Rofecoxib" <4>

Post-marketing studies are often initiated by the drug manufacturers at the explicit request of government regulators. Yet in the United States and in Canada questions have been raised about the legislative authority of drug regulatory agencies to mandate such studies. In the US, prior to the FDA Amendments Act of 2007 <6> it seemed unclear whether the Food and Drug Administration (FDA) had the legislative or regulatory authority to request post-marketing surveillance studies,<7> except in cases where a drug had been accelerated <8>. In Canada, Health Canada still considers it lacks the regulatory authority to explicitly impose post-marketing surveillance studies as a condition for further sales of a pharmaceutical product. Although governments often encourage pharmaceutical sponsors to conduct further research and may encounter a willingness to do so, calls from experts for further pharmaco-vigilance research on some contested products have remained unanswered.

As importantly, many have questioned the wisdom of relying on drug manufacturers to conduct post-marketing studies of their own products <9>. Studies indicating a statistical correlation between study outcomes and funding source, reports of misleading selection of trial designs, and the exposure of various instances of hiding negative data, data misrepresentation, ghost authorship and related practices, have added fuel to this concern <10, 11>.

Having the CIHR as the DSEN host could strengthen public confidence in the independence of the network as CIHR is not involved in drug approvals and has no direct financial interest in drug development. The CIHR has the status and connections to secure the commitment of qualified researchers who are independent from the products and the drug manufacturers. In their 2006 commentary on reforming [U.S.] drug regulation, Ray and Stein <11> call for the establishment of an independent specialized Center for Post-Marketing Studies, which would have the mandate to promote independent conduct of post-marketing studies with independent researchers. Prior to amendments to the US Food and Drug Act in 2007, there was discussion of needing an independent US agency or centre for post-market studies <7, 11, 12,> to avoid conflict of interest created by having those approving new drugs also conducting post-market studies on these same drugs. While the FDA Amendments Act (2007) <6> gave, among other things, the authority to the FDA to order drug manufacturers to conduct post-marketing studies, it stopped short of creating an independent agency for post-marketing drug trials.

While we believe that the establishment of a fully independent agency with post-marketing surveillance as a core mandate would be ideal, having the CIHR as the host of the DSEN moves Canada forward, provided that a couple of conditions are fulfilled. First, a good governance framework must be instituted that is based on a sound conflict of interest approach. Dealing appropriately with conflict of interest will provide researchers with the necessary environment for producing credible, honest, timely and scholarly research that can withstand academic and public scrutiny. Stringent conflict of interest rules and other measures that protect the independence of researchers are essential in this context because post-marketing surveillance research can have huge financial implications. The potential need to withdraw a blockbuster drug from the market, and potential legal liability related to findings of serious side-effects, create serious incentives that may impact behaviour. The 30% tumbling of Merck stock the day after the withdrawal of Vioxx from the market, decreasing its market value by an estimated \$ 26.8 billion, is a stark reminder of what interests are at stake <13 >.

Strong and enforceable conflict of interest rules for all those involved in the research, its reportage and knowledge translation (e.g., researchers, centres of excellence, and staff), and measures to protect researchers' independence are in our view crucial. Such rules and measures are needed because of the very significant public health implications of this type of research and the reasonable concern that the financial interests of industry sponsors in an already marketed product can lead to significant pressure on investigators, institutions and those working directly under contract with pharmaceutical sponsors. This is not to say that such pressure always affects researcher or institutional behaviour, but it is a reasonable expectation that such pressure can have this impact and can affect public trust.

Our support for CIHR as the DSEN host is conditional on the expectation that also the CIHR will be strongly independent from both the drug regulatory agency and industry as this is crucial for a

public funding agency that has a mandate to promote independent drug surveillance research. The commercialization mandate embedded within the statutory role of CIHR and the growing emphasis on CIHR-Industry partnerships does, in this context, create a certain tension. A major step forward for CIHR would be the adoption of an ethics policy on partnership with the for-profit private sector, discussed at a 2007 CIHR workshop <14>, which takes into account CIHR's hosting of the DSEN.

With respect to the DSEN itself, we believe some strong governance principles ought to be implemented to ensure independence of DSEN and researchers supported with DSEN funding. In the spring 2009, we presented a governance framework at a DSEN Workshop on Potential Legal and Ethical Risks <15> to address conflict of interest issues. We recommended that the DSEN governance and operational standards should be such that they promote five intertwined principles: 1) transparency; 2) accountability; 3) independence; 4) commitment to scientific integrity; and 5) freedom of action. Tables 1 and 2 (reproduced largely from our presentation) elaborate on the five key principles in the context of the DSEN governance and as applied to the researchers funded by DSEN.

There are many stakeholders who have a legitimate and material interest in the research priorities and their involvement can strengthen the DSEN. Thus, it is important that the DSEN engage the variety of stakeholders, including for example, patient/consumer groups, drug manufactures, Health Canada and other policy-makers. We believe the five key principles should set the stage for stakeholder engagement about research priorities. While having stakeholders contribute their views about research priorities will help inform the DSEN, membership on the DSEN Oversight Committee, the core governing body, should be carefully chosen to avoid concerns about conflict of interest. Members of the Oversight Committee should be fully independent from those who have financial interests in a marketed product and be balanced to avoid strong influence from those who have been involved in prior regulatory approval. While having the DSEN hosted within Health Canada would not have allowed for adequate independence, it is important that Health Canada provide input about research priorities which membership on the DSEN Oversight Committee would help them achieve. Finally, the DSEN should also be set up so that it is structurally independent within the CIHR from those who are involved in the creation of partnerships and the promotion of CIHR-industry collaboration.

We believe DSEN and CIHR can play a major role in securing the public's trust in post-marketing studies, but respect for and realization of the core principles set out earlier will be key. Recent statements of the current president of CIHR about the need to intensify collaboration between CIHR and industry, combined with the appointment of a Vice President of Pfizer Canada to CIHR's Governing Council--the first pharmaceutical representative to be appointed <16, 17>-- does raise the question whether the CIHR remains sufficiently independent from industry to host the DSEN. We therefore recommend that the CIHR and the Minister of Health,

to who the CIHR reports, carefully re-evaluate the impact of such appointments and of increased collaboration with industry on the independence of the DSEN.

We commend the CIHR in co-hosting the DSEN Workshop on Potential Legal and Ethical Risks <15> as a step forward and look forward to the release of the final DSEN governance structure and policy documents to see how they fit with what we believe are core principles for building public trust. The release should be imminent since the DSEN is not yet fully functional although the announcement of Catalyst Grants <18> suggests they are starting to stimulate research in post market drug safety and effectiveness.

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**Table 1: Principles for Good DSEN Governance Based on a Sound Conflict of Interest (COI) Approach**

1.	<p><u>1 Transparency and Openness</u></p> <p>Public disclosure of vital network information such as:</p> <ul style="list-style-type: none"> <li>- standards for evaluating the network</li> <li>- governance arrangements</li> <li>- standards for selecting researchers, staff and centres of excellence</li> <li>- standards for evaluating researchers</li> <li>- standards for obtaining and dealing with stakeholders input</li> <li>- standards re: sources and use of data</li> <li>- standard procedure for registration of clinical trials and results reporting</li> <li>- COI disclosures of all those in the network (officials, researchers, etc)</li> <li>- transparent procedures for dealing with COI</li> </ul>
2.	<p><u>Accountability:</u> Being subject to clear rules of behaviour and being publicly answerable such as:</p> <ul style="list-style-type: none"> <li>- Existence of clear governance arrangements; partnerships; agreements and policies for protecting academic values and the integrity of the network (including its data)</li> <li>- Efficiency and enforceability of policies and procedures (especially concerning COI, privacy and confidentiality)</li> <li>- DSEN COI Committee: clear authority over COI matters for all DSEN research; uniformity of COI standards for addressing COI across the network for DSEN related research</li> <li>- External verification and answerability: registering trials, publishing results independently and within a specific period of time</li> <li>- Accountability to CIHR</li> <li>- Accountability of centres of excellence to central DSEN administration</li> </ul>
3.	<p><u>Independence:</u> Autonomy from stakeholders, such as</p> <ul style="list-style-type: none"> <li>- Autonomy from commercial influences</li> <li>- Arms length from regulatory authorities in areas such as governance; budget; setting policies and enforcing them (especially COI and confidentiality); research priorities, selecting researchers; evaluating network officials and researchers; interpreting data and reporting</li> <li>- Elements: budgetary ‘independence’ (medium to long-term security); structural and human resources independence</li> <li>- clear rules about representation and conflicts of interest of public stakeholders</li> <li>- commitment to public interest promotion with protection against inappropriate capture by special interest groups</li> </ul>



4.	<p><u>Commitment to Scientific Integrity:</u> Dedication to scientific honesty, such as</p> <ul style="list-style-type: none"> <li>- Preserving scientific integrity and academic freedom including selecting researchers who will be as unconflicted as possible</li> <li>- Access to full data and appropriate control over it</li> <li>- Absence of legal constraints associated with access to data and use of data</li> <li>- Supporting the conduct of research that is consistent with academic values: unbiased, truthful and rigorous</li> </ul>
5.	<p><u>Freedom of Action:</u> de facto and de jure</p> <ul style="list-style-type: none"> <li>- Ability to act independently from commercial influences and being at arms-length from regulatory authorities, in the best interests of the public</li> <li>- Absence of constraints associated with potential liability for good faith actions (e.g., insurance; commitment of stakeholders to respecting independence researchers)</li> <li>- Absence from legal constraints flowing from contracts or arrangements that affect the ability (or the perception of ability) to meet its commitment to the network principles (accountability and openness; accountability; independence; commitment to scientific integrity; freedom of action)</li> </ul>

Table 2: Principles for Dealing with Researcher conflict of interest and conflict of interest of the researchers' host institution

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1.	<u>Transparency and Openness</u> <ul style="list-style-type: none"> <li>- full disclosure of potential, actual or perceived COI situations of researcher (and his/her family)</li> <li>- balancing access to information on COI and privacy interests individuals</li> <li>- creation of transparent structure and reliable oversight of COI</li> </ul>
2.	<u>Accountability</u> <ul style="list-style-type: none"> <li>- avoidance of COI situations if possible</li> <li>- adherence to network COI policies and procedures</li> <li>- enforcement of COI rules and sanctions</li> <li>- introduction of 'presumption' that researchers cannot have COI and clear rules for when exceptions are appropriate and needed</li> </ul>
3.	<u>Independence</u> <ul style="list-style-type: none"> <li>- maintaining monetary (actual, perceived or future) independence and academic independence from commercial influences and remaining at arms length from regulatory authorities</li> <li>- procedures to deal with centres of excellence's host institution's COIs and potential impact on researcher COI;</li> <li>- role of DSEN in strengthening researcher independence in situations of centres of excellence's host institutional COI</li> <li>- protection of researchers against threat of legal procedures by pharmaceutical sponsors for DSEN-related research.</li> </ul>
4.	<u>Scientific Integrity:</u> <ul style="list-style-type: none"> <li>- conduct research that is consistent with academic values (e.g., remaining impartial and truthful, conducting rigorous evaluations with scientific merit, adhering to protocols, publishing/disseminating findings)</li> <li>-provide education and support of DSEN researchers (e.g., education on COI issues and DSEN standards for dealing with them, support of independence of researchers, raising awareness of importance of structural independence)</li> </ul>
5.	<u>Freedom of Action</u> <ul style="list-style-type: none"> <li>-remain free to conduct research that has scientific integrity and that is consistent with network responsibilities, policies and procedures</li> <li>-remain free to act in the best interests of the public</li> </ul>