

# Drug Safety and Effectiveness Network



## Framework for the Management of DSEN Queries



Canadian Institutes  
of Health Research

Instituts de recherche  
en santé du Canada

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## **Table of Contents**

### **1. Objectives**

### **2. Background**

### **3. Scope**

### **4. Procedures for the Management of DSEN Queries**

4.1 Identification and Submission

4.2 Initial Examination

4.3 Feasibility Assessment

4.4 Prioritization

4.5 Research

4.6 Dissemination

4.7 Maintenance

### **5. Contact Information**

#### **Appendices**

Appendix 1 – Process for the Management of DSEN Queries

Appendix 2 – Template for Summarizing Information on DSEN Queries

Appendix 3 – Multi-Criteria Decision Analysis Framework

Appendix 4 – Relevant Research Areas of the DSEN Collaborating Centres

Appendix 5 – Frequently Asked Questions



## **List of abbreviations used throughout the Guidance Document**

<b>ADR</b>	Adverse Drug Reactions
<b>CADTH</b>	Canadian Agency for Drugs and Technologies in Health
<b>CC</b>	DSEN Collaborating Centre
<b>CIHR</b>	Canadian Institutes of Health Research
<b>CO</b>	DSEN Coordinating Office
<b>DSEN</b>	Drug Safety and Effectiveness Network
<b>F/P/T</b>	Federal / Provincial / Territorial
<b>MCDA</b>	Multi-Criteria-Decision Analysis approach
<b>RCT</b>	Randomized controlled trial
<b>RTs</b>	DSEN Research Teams
<b>SAC</b>	Science Advisory Committee
<b>SC</b>	DSEN Steering Committee
<b>WG</b>	Federal and Provincial Working Group on Prioritization of DSEN Queries

## **1. Objectives**

The purpose of this document is to provide a clear description of the processes used for the management of *Drug Safety and Effectiveness Network Queries (DSEN Queries)* on the safety and effectiveness of drugs on the Canadian market. The management of these DSEN Queries involves steps and elements for the identification and submission of the queries, as well as the feasibility assessment, prioritization, research, knowledge translation, and maintenance of topics relating to the safety and effectiveness of marketed drugs.

## **2. Background**

In Canada and worldwide, more information is needed on the safety and effectiveness of drugs used by diverse patient populations in real-world settings, outside the controlled experimental environment of clinical trials. Therefore, the *Drug Safety and Effectiveness Network (DSEN)* has been established at CIHR as part of the Government of Canada's *Food and Consumer Safety Action Plan*. CIHR is collaborating with Health Canada in the development of the Network, together with stakeholders from across Canada. The main objectives for establishing the DSEN are to increase the evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and patients; and, to increase capacity within Canada to undertake high-quality post-market research in this area.

The DSEN has three key components:

- The *DSEN Steering Committee (SC)* which provides strategic direction to the DSEN and set priorities for needed research through the development of the *prioritized research agenda*
- The *DSEN Coordinating Office (CO)* established within CIHR to facilitate and coordinate network operations; and
- A virtual national network of research teams focusing on post-market pharmaceutical research as proposed by DSEN stakeholders through DSEN Queries

A DSEN Query is defined as:

*A focused, well defined question identified by healthcare decision-makers, as a gap in evidence on the safety and effectiveness of prescribed drugs on the Canadian market, that can be addressed through DSEN sponsored research and that could result in increased knowledge in ensuring the ongoing safety and effectiveness of these medicines in a “real world” environment.*

DSEN Queries could be identified by a number of sources including decision-makers within the federal regulator or the federal/provincial/territorial (F/P/T) drug plans. Subsequently, the Queries will be evaluated and prioritized by the SC in the development of the *prioritized research agenda* for the DSEN.

The research generated in response to the DSEN Queries is intended to bridge the gap in evidence between the validated “proof of concept” and the needed “proof of value” for drugs on the Canadian market. This will be achieved through increasing the knowledge of these drugs which can be used to inform decisions in areas intended to ensure the drugs are performing in

the “real world” health environment, providing tangible benefit without unacceptable levels of risk.

*This document has been prepared to assist stakeholders in understanding the submission of DSEN Queries for prioritization by the DSEN Steering Committee. It is intended to provide clarity and transparency on the process and make tools available in the form of standardized procedures and templates. This, in turn, is expected to promote efficiencies in the overall process and facilitate the submission of queries.*

### 3. Scope

This document applies to potential DSEN Queries on the safety and/or effectiveness of prescribed drugs on the Canadian market. Although information and datasets generated in an international context could be considered while conducting the research in this area, this document does not apply to potential queries or research topics on drugs marketed outside Canada.

DSEN attends to the gap in information on the safety and effectiveness of Prescription Drugs (biologics and pharmaceuticals) used in the real-world. Over-the-counter Drugs, Medical Devices and Natural Health Products (including vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines such as traditional Chinese medicines, probiotics, and other products such as amino acids and essential fatty acids) are presently not addressed under DSEN’s mandate.

### 4. Procedures for the Management of DSEN Queries

This section outlines details and considerations for the various steps in the procedure. A schematic is available illustrating the flow of these steps and procedures (see *Appendix 1*).

#### 4.1 Identification and Submission

Identification of a potential research question is not sufficient in and of itself to be submitted directly to DSEN. At present, DSEN Queries are those potential research questions submitted by high level decision makers working within the Federal Regulator, a F/P/T drug plan or organizations mandated to support F/P/T decision making with respect to drugs (e.g. Canadian Agency for Drugs and Technologies in Health [CADTH]).

Examples of DSEN Queries on the real-world safety and effectiveness of drugs could include (but are not limited to) topics seeking additional information on:

- Comparing of two (or more) existing drugs (effectiveness and/or safety issues)
- Full target population for the marketed drug
- Long-term outcomes

#### Parties eligible to submit a DSEN Query:

- Federal regulator
- F/P/T drug plans
- Organizations mandated to support F/P/T decision making with respect to drugs (e.g. CADTH)

#### Parties not eligible to submit directly a DSEN Query at the moment:

- Voluntary Health Organizations
- For profit enterprises (e.g. drug manufacturers, private insurance providers)
- Individual practitioners
- Community pharmacies
- Public (e.g. patients and or consumer organizations)

- Drug interactions
- Inputs for pharmacoeconomic models
- Support for “willingness to pay” models

Query Submission

Stakeholders identifying a potential DSEN research question should complete to the best of their ability, the template available in the **Appendix 2 – DSEN Query Summary**, summarizing the various elements of the issue(s) relating to their potential DSEN research question.

The template asks a series of questions for capturing the relevant information on a DSEN Query that will be subsequently used by the SC in the prioritization process (refer to *Appendix 1*) and ultimately used as a reference source of information for DSEN affiliated researchers in conducting the research on the topic.

At various points in the process, clarification and/or additional information from the Query Submitter may be needed on their DSEN Query. As such, it is important that a contact be clearly identified for the potential research topic (as specified in *Appendix 2*).

To minimize delay in processing your Query, please complete this form to the best of your ability within a maximum of 5 pages (not including any references you deem pertinent).

Once completed, the DSEN Query Summary is to be submitted to the CO:

by e-mail to: [DSEN-RIEM@cihr-irsc.gc.ca](mailto:DSEN-RIEM@cihr-irsc.gc.ca)

by mail to: Drug Safety and Effectiveness Network  
Canadian Institutes of Health Research  
160 Elgin Street, 9th Floor  
Address Locator 4809A  
Ottawa, ON  
K1A 0W9

Expedited procedures:

Mechanisms will be established to identify and expedite DSEN Queries of an urgent nature (e.g. typically relating to drug safety issues). As such, Query Submitters are requested to identify their potential DSEN Query according to one of the following categories (as outlined in the template provided in *Appendix 2*):

- Safety
- Comparative Effectiveness
- Urgent Request

#### 4.2 Initial Evaluation

The CO will conduct an initial evaluation of the DSEN Query to determine if sufficient information has been provided to allow for an appropriate understanding of the issue(s) for subsequent steps. If additional information is warranted, the CO will seek clarification/additional information from the Query Submitter.

### **Examples of strong and weak queries**

**Weak question:** *Study the safety of second-generation antipsychotics in seniors*

**Why:** *The question isn't defined well enough, the population is very large, and there are many drugs that need to be considered.*

**Strong question:** *Study of second-generation antipsychotics in the management of dementia in institutionalized seniors*

**Why:** *The question provides a defined population, and a dataset that will enable a reasonable answer to be provided.*

DSEN Queries that are sufficiently complete for proceeding to the subsequent steps in the process will be entered into a record system managed by the CO.

### **4.3 Feasibility Assessment**

All DSEN Queries will undergo a *Feasibility Assessment* prior to being forwarded to the SC for consideration.

Under the Feasibility Assessment, a *Science Advisory Committee (SAC)*, which brings together researchers, who have expertise in several disciplines and methodologies from across the DSEN network will assess the scientific feasibility of each Query (*i.e.*, determine the possible approaches for responding to Queries including methodologies, project duration, availability of data, costs). The SC will take into consideration the analysis flowing from the SAC to establish the *prioritized research agenda*.

### **4.4 Prioritization**

The SC acts in an advisory capacity to the DSEN with respect to the program's strategic direction and priorities for research. Among its activities, work of the SC will include the selection and prioritization of research to address identified information needs into a prioritized research agenda. The SC meets regularly to discuss, evaluate, and

prioritize the potential research queries that have been received.

To assist the SC in their role, a Multi-Criteria-Decision-Analysis (MCDA) approach is used to inform the prioritization of Feasible Queries. This decision framework approach is designed to address multiple objectives and allows a rating of Queries, providing rigorous, transparent and reproducible information to the SC upon which prioritization can be advised.

The DSEN MCDA framework (criteria, criteria definitions, weights and rating scales), was developed by an independent working group (WG) of representatives from Provincial/Territorial drug plans and Health Canada. The MCDA scoring tool provided in *Appendix 3* has been reviewed and approved for use by the SC.

The WG reviews and rates Queries on the basis of the MCDA derived scoring tool. This involves:

- Reviewing the information provided in the Query submission on the expected impact for each criterion
- Assigning a score for each criterion based on the reviewed description of the expected impact, by applying the rating scale by consensus
- Calculating a composite score for each submission, using the criteria weights

**A MCDA implementation**  
*started with the determination of criteria pertinent to the issues and objectives related to the decision to be made. Once criteria were identified, each criterion was defined so as to ensure consistent interpretation of what is being measured. Then each criterion was assigned a weight. Finally, each criterion was attributed a rating scale that flowed from the criterion definition and allowed consistent rating of potential impact.*



- Ranking submissions based on composite score

The result of this phase of the process will be a composite rating for each Query which represents a summary of the expected impact of conducting research related to the Query. Composite ratings are comparable across all submissions.

The SC will then deliberate and make the final recommendations to advance DSEN Queries to the *prioritized research agenda* based on the ranked list of queries as submitted by the WG.

Upon receipt of the final recommendations by the SC on the Query, the CO will inform the Query Submitter of the status with any available supplementary information (e.g., proposed query has/has not been accepted for the prioritized research agenda). At such time it will also be possible for the CO to post the updated DSEN prioritized research agenda to its website.

#### 4.5 Research

According to the SC recommendations and the prioritized research agenda, DSEN Queries may be taken on by one or several DSEN Research teams (RTs). Other queries that could not be undertaken by RTs may be made open to investigation by the larger scientific community by the means of CIHR Funding Opportunities.

The RTs form a coordinated national network of over 150 researchers in post-market drug safety and effectiveness committed to the highest excellence in research. Made up of existing data centres, teams and networks from across Canada, the RTs create the research capacity to respond in a timely manner to the drug safety and effectiveness queries of decision makers.

The RTs have been established in principal thematic areas of research methodologies, each supporting distinctive competencies within the national DSEN initiative (see *Appendix 4*). These include the:

- Canadian Network for Observational Drug Effect Studies (CNODES)
- Collaborating Centre for Prospective Studies consisting of three distinct Research Teams working in thematic areas:
  - DSEN Active Surveillance and Evaluation of Adverse Drug Reactions in Canadian Healthcare Team (SEARCH)
  - Pharmacogenomics of Adverse Events National Team (PREVENT)
  - Canadian Network for Advanced Interdisciplinary Methods for Comparative Effectiveness Research (CAN-AIM)
- Collaborating Centre for Network Meta-Analysis consisting of three distinct RTs:
  - DSEN Knowledge Synthesis Research Unit (KSRU)
  - DSEN Network Meta-analysis Team (NETMAN)
  - Team for Network Meta-analysis (TNMA)

#### **Examples of strong and weak queries**

**Weak question:** *Does Drug A have similar cardiotoxic effects and mechanism of action as Drug B using the same animal model?*

**Why:** *Not within scope of DSEN as research would require animal studies (it is not a clinical study)*

**Strong question:** *How does Drug A compare to Drug B in terms of effectiveness and safety for anticoagulation in atrial fibrillation?*

**Why?** *The question refers to specific drugs for a defined health problem.*

#### **4.6 Dissemination**

DSEN is organized as an integrated knowledge translation research entity. Among its goals is one of bringing together researchers and the users of research knowledge in order to target research that is directly applicable to decision making with respect to the safety and effectiveness of drugs used by Canadians. Thus dissemination of research results immediately upon conclusion of a research investigation back to those who originally proposed a DSEN Query is of paramount importance and an agreed principle of DSEN affiliated researchers.

DSEN research results will remain the intellectual property of the researchers who developed the evidence. In many cases it will be necessary that the research results be transmitted in confidence until such time as the results are submitted for publication in the academic literature. DSEN, a CIHR program, complies with the CIHR Policy on Access to Research Outputs. Under this policy, researchers awarded new or renewed funding from CIHR are reminded to adhere with the following responsibilities:

- ensure that all research papers generated from CIHR funded projects are freely accessible through the Publisher's website or an online repository within six months of publication;
- deposit bioinformatics and molecular coordinate data into the appropriate public database (e.g. gene sequences deposited in GenBank) immediately upon publication of research results;
- retain original data sets for a minimum of five years (or longer if other policies apply); and
- acknowledge CIHR support by quoting the funding reference number in journal publications.

#### **4.7 Maintenance**

All DSEN Queries, the results of the assessments stemming from their management, as well as records of resulting knowledge translation activities involving DSEN funded research will be maintained by the CO.

### **5. Contact Information**

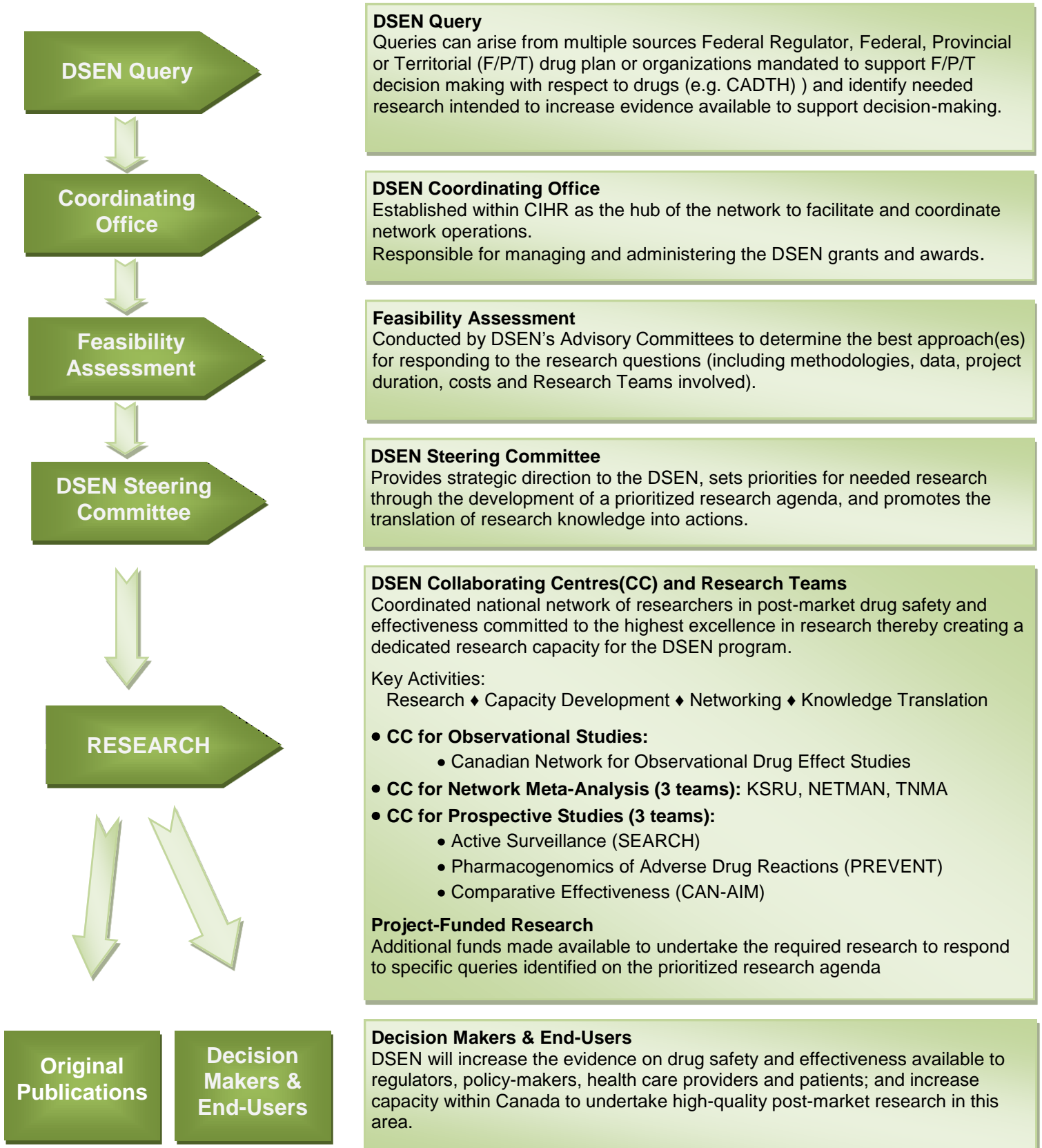
Please contact us for additional information about the DSEN Initiative, the management of the Queries or on how to submit a Query at:

- [dsen@cihr-irsc.gc.ca](mailto:dsen@cihr-irsc.gc.ca)
- 613-948-2786

or visit our website at <http://www.cihr-irsc.gc.ca/dsen.html>



## Appendix 1 – Process for the Management of DSEN Queries



## Appendix 2 – Template for Summarizing Information on DSEN Queries

DSEN QUERY SUMMARY	
DSEN Query Title:	
DSEN Reference Number:	
Submitted by (organization):	
Contact Information:	<ul style="list-style-type: none"> <li>• Name</li> <li>• Phone</li> <li>• E-mail</li> </ul>
Proposed DSEN Query Category(ies):	<input type="checkbox"/> Safety <input type="checkbox"/> Comparative Effectiveness <input type="checkbox"/> Urgent Request
DSEN Query Proposal	
1.	<b>What is the specific DSEN Query (in the form of a research question)?</b> (If possible, please state the question in terms of <u>specific &amp; measurable objectives</u> , including any pre-specified hypotheses. Ideally, the research objectives would define the intervention(s), clinical problem, population and outcome.)
2.	<b>What is the relevant information regarding the drug product(s) for which the DSEN Query is being proposed?</b> <i>Please provide the:</i> 2.1 name (brand/generic) 2.2 product class 2.3 indication(s) or use(s) of the product and severity of the underlying condition/clinical problem considering risk of death, pain and psychological effects. 2.4 anticipated number of patients that are using or will use the drug 2.5 other noteworthy information about the drug product as appropriate
3.	<b>What is the knowledge gap that is going to be addressed with this DSEN Query?</b> <i>Please consider the:</i> 3.1 degree of urgency for decision makers to obtain new information, 3.2 usefulness of information to decision makers, and 3.3 number of decision makers who could use this information.
4.	<b>What is the current level of evidence available on this issue?</b> <i>Considering previous research in the particular area:</i> 4.1 how critical is the evidence gap to be filled, and 4.2 the likelihood of findings to lead to change in patient health status including safety, effectiveness and comparative effectiveness?
5.	<b>How might the information generated by DSEN research be used by your organization?</b> <i>What is the potential of research findings to:</i> 5.1 be translated into new regulatory, clinical or health service practice 5.2 contribute to cost effective management of the condition or health problem
6.	<b>Are there broader implications of generating the information through DSEN research? (e.g. are there any legal, ethical, equity, political or social implications related to the Query)</b>

To minimize delay in processing your Query, please complete this form to the best of your ability within a maximum of 5 pages (not including any references you deem pertinent).

DSEN Query Summaries should be submitted:

by e-mail to: DSEN-RIEM@cihr-irsc.gc.ca

by mail to

Drug Safety and Effectiveness Network  
Canadian Institutes of Health Research  
160 Elgin Street, 9th Floor  
Address Locator 4809A  
Ottawa, ON, K1A 0W9

## Appendix 3 Prioritization Criteria Package

CRITERIA	DEFINITION	WEIGHT	RATING			
			0	1	2	3
1. Extent of the drug use in Canada	Anticipated number of patients that are using or will use the drug	13	Less than 5,000	5,000 to 99,999	100,000 to 999,999	More than 1,000,000
2 - Severity of condition or health problem	Severity of the underlying condition or health problem considering risk of death, pain and psychological effects	8	Minimal impact on morbidity or mortality	Short term condition with moderate impact on morbidity or mortality	Chronic condition with moderate impact on morbidity or mortality	Significant impact on morbidity or mortality
3- Potential to change health outcomes in real-world use	Likelihood that research findings will lead to change in patient health status including safety, effectiveness and comparative effectiveness	17	No likelihood of impact of research findings	Low likelihood of impact of research findings	Moderate likelihood of impact of research findings	High likelihood of impact of research findings
4- Responsiveness to decision-makers	The following three aspects are to be considered: degree of urgency in obtaining the new information from the perspective of decision-makers; usefulness of information for decision makers; number of decision makers that could use this information	14	Low impact in terms of all aspects	Moderate impact in terms of at least one aspect	Significant impact in terms of at least one aspect or moderate impact on all three aspects	Significant impact in terms of all three aspects
5- Public demand issues	Research investigation will consider extra evidentiary pressures such as legal, ethical, equitable, political and social issues	10	Query does not involve consideration of any legal, ethical, equity, political or social implications	Query involves minimal consideration of at least one of legal, ethical, equity, political and/or social implications	Query involves moderate consideration of at least one of legal, ethical, equity, political and/or social implications	Query involves significant consideration of at least one of legal, ethical, equity, political and/or social implications
6- Knowledge translation	Potential of the research findings to be translated into new regulatory, clinical or health services practice	8	Research findings are not expected to translate into regulation, or clinical or health services practice	Minimal likelihood that the research findings will translate into regulation, or clinical or health services practice	Moderate likelihood that the research findings will translate into regulation, or clinical or health services practice	Significant likelihood that the research findings will translate into regulation, or clinical or health services practice
7- Cost of producing the evidence	Proposed budget total in the Query submission	4	More than \$5,000,000	\$1,000,000 to \$4,999,999	\$100,000 to \$999,999	Less than \$100,000

*Framework for the management of DSEN Queries  
Drug Safety and Effectiveness Network (DSEN)*

8- Cost effective management of the condition or health problem	Potential of the research findings to contribute to the cost effective management of the condition or health problem	15	No expected impact on the cost of managing the condition or health problem	Minimal expected impact on the cost of managing the condition or health problem	Moderate expected impact on the cost of managing the condition or health problem	Significant expected impact on the cost of managing the condition or health problem
9- Need for additional evidence	Considering previous research in the particular area, how critical is the evidence gap to be filled	11	Not a critical gap	Minimally critical gap	Moderately critical gap	Significantly critical gap

**EXPLANATORY NOTE:** Minimal, moderate and significant in the context of the rating scale are meant to divide the range of possible outcomes for each applicable criterion into three equal parts. For example, a rating of significant would be assigned to an outcome deemed to be in top third of possible outcomes.

## **Appendix 4 - Relevant Research Areas of the DSEN Collaborating Centres (CCs) and Research Teams (RTs)**

Within their own research area, the CCs and RTs may, for example, undertake studies on the following:

### **Collaborating Centre for Observational Studies:**

- Perform drug safety and effectiveness research using epidemiological approaches and existing national healthcare databases
- Analyze, link, and develop electronic health data for research

### **Collaborating Centre for Prospective Studies:**

- **Active Surveillance**
  - Active safety surveillance of post-market drugs using valid epidemiologic study designs
  - Working with established disease, or patient registries to assess the benefit to harm profile for drugs of interest in a “real world” context
  - Active surveillance by gender and/or in different patient subpopulations such as ethnic and racial minority population, children or seniors
- **Pharmacogenomics of Adverse Drug Reactions (ADRs)**
  - Assessments on the potential role of pharmacogenomics relating to the impact on reduction of incidence of ADRs
  - Validation of surrogate outcome measures and real world studies
  - Identification of predictive genomic biomarkers of drug risks
  - Compare incidence of ADRs by gender and/or in different patient subpopulations such as ethnic and racial minority population, children or seniors
- **Comparative Effectiveness**
  - Performing studies comparing the clinical effectiveness, risk and benefits of treatment options in different patient subpopulations or circumstances
  - Developing strategy, best practices and methods for comparative effectiveness research in the “real world”

### **Collaborating Centre for Network Meta-Analysis:**

- Indirect comparisons (e.g. mixed treatment comparisons) of drugs of interest using data from previously completed RCTs
- Innovative methods for systematic reviews

## Appendix 5 – Frequently Asked Questions

**1. Will DSEN (the Drug Safety and Effectiveness Network) now become, de facto, responsible for whether an unsafe drug is on the Canadian market?**

No, responsibility for determining the ongoing market authorization of a drug resides with the federal drug regulator, which is Health Canada. Results of DSEN research will provide an independent source of additional information that can be used by the federal decision maker in ongoing health product vigilance activities to assess the risk-benefit balance of marketed health products in real-world settings.

**2. Why is DSEN hosted at CIHR instead of Health Canada which is the Canadian drug regulator?**

The Canadian Institutes of Health Research (CIHR) was chosen to host DSEN because of its status as an independent agency, as well as its focus on research, available clinical skills, experience in managing the funding of research and training, as well as its national and international reputation.

**3. Will DSEN determine which drugs should be paid for by public insurance?**

No, decisions are made by payers based upon many information inputs. DSEN research will provide an additional independent source of information that can be used by payers regarding their decisions.

**4. Will DSEN accept funding from Drug Companies?**

No. DSEN research is funded entirely by the federal government through CIHR.

**5. Who decides what drugs need to be researched?**

DSEN has a Steering Committee which determines the research priorities of the network amongst questions deemed relevant to their information needs by decision makers.

**6. What is the role of the DSEN Coordinating Office?**

The function of the DSEN Coordinating Office is to facilitate the interaction between decision makers and the researchers participating in the Collaborative Centres (CC) and Research Teams, by assisting in the alignment of the research activities of the CCs with the prioritized research agenda established with the SC. The DSEN Coordinating Office is charged with administering the DSEN grants & awards budget and developing appropriate mechanisms to facilitate, foster, support and maintain the relationship to be established between the decision makers and the research community.

**7. Will DSEN research results be published for everyone to read?**

Yes, DSEN is committed to having the results of its research publicly available through open access publications and its website. As part of CIHR, DSEN adheres to the principle that greater access to research publications and data will promote the ability of researchers in Canada and abroad to use and build on the knowledge needed to address significant health challenges. Open access enables authors to reach a much broader audience, which has the potential to increase the impact of their research.

**8. What products are covered by DSEN's mandate?**

DSEN attends to the gap in information on the safety and effectiveness of *Prescription Drugs* used in real-world. *Over-the-counter Drugs*, *Medical Devices* and *Natural Health Products* are presently not addressed under DSEN's mandate.



**9. How many questions/year will be submitted to the Collaborating Centres such as the CNODES?**

We don't know. It will depend on the prioritized research agenda set by the SC and on the scope of the projects, the queries could span multi-month to multi-year projects.

**10. Where can I find information about DSEN?**

On CIHR's website at: <http://www.cihr-irsc.gc.ca/dsen.html> or by email: [dsen-riem@cihr-irsc.gc.ca](mailto:dsen-riem@cihr-irsc.gc.ca)