Canadian Network for Observational Drug Effect Studies (CNODES)

Project Guide

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1. Project Team Formation

As soon as DSEN gives CNODES the official go-ahead on a specific query, the immediate next step is to put together a complete and well-rounded Project Team. The composition of the Project Team is the responsibility of the Database Team. The Coordinating Centre, which facilitates this process, sends a call-out to the Steering Committee requesting nominations for Project Team membership. Steering Committee members are responsible for ensuring that all nominated members of the Project Team from their site are well informed regarding the roles and responsibilities of the position they are committing to. The roles and responsibilities of each Project Team member are described in Section 4.

Note: In the event that the Steering Committee decides to first conduct a pilot study (e.g., involving 1-2 sites), the call-out for the team would only take place after the results of the pilot study are reviewed and approved by the Steering Committee and a decision to pursue the full study is made.

Typically, a CNODES Project Team includes the following members:

- Project Lead
- Site Liaisons (one per participating site)
- Methods Liaison
- Content Liaison (if the required expertise is not already available on the team)
- Steering Committee Liaison (if needed)
- Lead Analyst
- Site Analysts (one per participating site)
- Representative(s) of the Query Submitter

Note: The Project Lead, Liaisons, and Lead Analyst are the named authors of the corresponding manuscript. See CNODES Publications Policy.

Note: The Project Lead nominates the Lead Analyst, who is approved by the Database Team.

Once a Site Lead has submitted their nomination(s), the nominated Project Team member is requested to submit the following information to the Coordinating Centre:

- Their complete contact information, title, and affiliation
- A short, one paragraph biography, including their area of expertise
- A completed project-specific CNODES conflict of interest (COI) disclosure form (even if they have already completed the yearly COI form). Please refer to the CNODES COI policy for more information.

- A list of the people from their site whom they plan to work with on this project, including titles, affiliations, contact information, and a brief explanation of their intended role on the project (i.e., analyst, area specialist, etc.)

All liaison biographies and COI declarations are reviewed by the CNODES COI Committee and by the Project Team Lead prior to the start of a study as described by the CNODES COI Policy.

Once these steps are completed, the Database Team Lead accepts and confirms team membership.

2. Roles and Responsibilities

CNODES Project Teams generally consist of 10-12 individuals, with other collaborators contributing at each of the participating sites. Clear and frequent communication, the understanding of each member's roles and responsibilities, and the respecting of timelines is thus crucial to the successful and timely completion of these collaborative endeavors.

a. Project Lead

It is the Project Lead's principal duty to work with their Project Team to answer the query that was assigned to them and to put forth all efforts necessary to advance the project in a productive, efficient, and collaborative manner.

At the start of a project, the Lead is expected to introduce themselves to their Project Team (by email) and lay out the proposed project timeline, specifying when they expect a first draft of the scientific protocol to be ready. The first Project Team meeting generally takes place by teleconference and is organized with the assistance of the Coordinating Centre.

The Project Lead then works in conjunction with the Coordinating Center to draft a study timeline, which is provided to DSEN and the Query Submitter.

The Project Lead is responsible for the drafting of the scientific and analytical protocols. They are assisted by a protocol writing team (please refer to sections 4 and 6 of this Project Guide for a detailed description of these processes). The Project Lead is also responsible for ensuring that the scientific and analytical protocols are up-to-date, with amendments and clarifications added as needed, and informing the team when updated protocols are available.

Throughout the project, it is the responsibility of the Project Lead to remain in continuous communication with:

- The CNODES Research Coordinator, keeping the Research Coordinator up to date on the advancement of the project, changes in timelines, and any difficulties that are encountered or anticipated.

- The Project Team, via frequent updates by email or by organizing conference calls at every stage (especially during analysis), providing team members with opportunities to discuss and ask questions. **CNODES policy requires that the Project Lead must contact the Project Team once a month at a minimum**, even if just to re-iterate the status quo.
- The Methods Liaison, as they collaborate on the drafting of protocols, review of results and meta-analysis of site specific results, as necessary.
- The Representative(s) of the Query Submitter, who the Project Lead and/or Research Coordinator include in team communications as appropriate.

It is the Project Lead's responsibility to chair Project Team meetings and teleconferences and prepare the agendas and finalize the minutes for these meetings. These minutes, which are taken by the Research Coordinator and include appropriate action items, are circulated to the Project Team and Coordinating Center.

The Project Lead works with the Research Coordinator to prepare the project description for public registration of the scientific protocol at www.clinicaltrials.gov (see Protocol Registration section below).

The Project Lead presents results to the Steering Committee and chairs the Project Team debriefing sessions (see section 9). In addition, the Project Lead presents the study results to the Query Submitter via teleconference arranged by the Coordinating Centre and writes the final report to the Query Submitter.

The Project Lead is expected to be the lead author of the manuscript (though they may delegate this responsibility and corresponding first authorship to another member of the Project Team) which they prepare with the assistance of a writing team and the remaining members of the Project Team. For more details on this process, please see section 10. Furthermore, it is the responsibility of the Project Lead to submit the manuscript to a journal and act as the primary contact for the submission.

The Project Lead also plays a key role in knowledge translation (KT) activities. This includes completing all required final reports (see section 11), participating in the KT messaging team, drafting the press release and frequently-asked questions (assisted by the KT messaging team), and serving as the main national and international spokesperson to media once the paper is published.

b. Methods Liaison

The Methods Liaison's role is crucial to the successful completion of CNODES projects. They are highly involved in working with the Project Lead in developing study protocols and proposing the most appropriate methodological approach to answer the DSEN query. They provide methodological expertise to the Project Team, help draft the scientific and analytical protocols, review site-specific analyses, and conduct the meta-analysis of site-specific results. In cases where the Methods Liaison is unable to perform the meta-analysis, the Methods Liaison must

alert the Project Lead and Methods Team Lead to this during protocol development. Finally, the Methods Liaison should report progress on a regular basis to the Methods Lead and consult with the Methods Lead should problems arise.

c. Site Liaison

The Site Liaison is the primary Project Team member for their site and is expected to lead the project ***at their site***. The Site Liaison is included in the Project Team listserv and has access to the document sharing system (i.e., Dropbox) and is thus expected to keep up to date on the status of the project, protocol changes, and study timelines. It is the responsibility of the Site Liaison to actively participate in the project, attend all meetings, and participate in teleconferences and relevant email exchanges. If they are unavailable to attend a teleconference or meeting, it is their Site Lead that generally attends in their place. In addition, as the acting point person at their site, they are responsible for relaying all necessary information and documents to their respective site team, including their analyst(s) and Site Lead. Site Liaisons are named authors of the corresponding manuscript and may also be called upon to assist in the drafting of the Final Report to the Query Submitter and the presentation of this report via teleconference (see sections 9 and 10). Ultimately, their responsibilities are equivalent to those of a principal investigator on a single centre study.

Specifically, the Site Liaison's responsibilities are to:

- Critically review all protocols, assemble the reviews and comments from relevant personnel at their site (including both analyst and Site Lead) and include them as part of their review of the protocols;
- Ensure that their Site Lead is up-to-date on the status of the project;
- Obtain research ethics board approvals and provide the confirmation of this approval (and any annual renewals) to the Project Lead and Research Coordinator;
- Be aware of and take responsibility for all their data custodian reporting requirements (e.g., approvals, small cell suppression, appropriate documentation in manuscripts [see CNODES Publications policy], pre-publication review, etc.);
- Obtain any necessary data custodian approvals and provide the required confirmation of approvals to the Project Lead and CNODES Coordinating Centre;
- Provide the Project Lead and/or Research Coordinator with a description of relevant formulary restrictions in their jurisdiction;
- Provide active and direct supervision of the analyst at their site as they implement the analytical protocol;
- Communicate with the Project Lead, Methods Liaison, and other members of the Project Team as questions arise during the conduct of site-specific analyses;
- Review all results prior to their posting in Dropbox;
- Provide the Project Lead with a list of site-specific protocol amendments (compiled by the Site Analyst) following the completion of site-specific analyses (see section 7);
- Be actively involved in the writing and review of the corresponding manuscript;
- Thoroughly review the manuscript with their team and provide one set of comments/revisions on behalf of their site.

In the event that results from their site are questionably different with those of other sites, the Project Lead may request a thorough review of analyses conducted to date; the Site Liaison is expected to thoroughly investigate these discrepancies and supervise additional analyses, if necessary, with the involvement of the Site Lead.

Following the submission of the manuscript for publication, a KT messaging team prepares a press release and other KT material. Site Liaisons may be invited to join this KT messaging team and are called on to review the press release and other KT material. Once a manuscript is accepted, Site Liaisons can nominate themselves to serve as a local spokesperson (i.e., spokesperson for local media) and may be invited to serve as one of the 3-4 national/international spokespeople for the project. All spokespeople must undergo a media training to ensure that all KT contains the CNODES approved message and is consistent across all sites.

d. Site Analyst

Each site nominates an analyst, whose primary responsibility is to perform the site-specific analyses required for the project. Site Analysts are included in all email exchanges as well as all meetings. Analysts are encouraged to participate in teleconferences and to review drafts of protocols; their comments are to be provided to their Site Liaison, who then includes their comments as part of their feedback.

Analysts are required to be members of the analyst group (and thus included in the analyst group listserv) throughout the conduct of the project.

Finally, the site analysts are responsible for the documentation of all site-specific protocol adaptations, which are provided to the Project Lead by the Site Liaison following the completion of the site-specific analyses (see Section 7).

Each site can choose to work with more than one analyst on any given project. However, in order to keep the teams manageable, the primary team members include one liaison and one analyst per site.

e. Lead Analyst

The Lead Analyst is nominated by the Project Lead and approved by the Database Team. In addition to their responsibilities in the conduct of site-specific analyses, the Lead Analyst assists the Project Lead in the analytical components of the project. This includes writing sections of the analytical protocol, reviewing early drafts of both the scientific and analytical protocols, writing required SAS code for inclusion in the analytical protocol, providing suggestions on the implementation of proposed methods, and serving as a reference person for other analysts participating in the project. Should the Lead Analyst require assistance, the Analyst Group Coordinator, who is located at the Coordinating Centre and included in the Project Team listserv, is available for consultation. Since the Lead Analyst is an author of the manuscript, they are also required to complete a COI Disclosure Form.

f. Content Expert

One or more content experts may be added if specific content area expertise that is required for the successful completion of the project is not found among members of the Project Team. This individual is nominated using the same procedures as other team members (described above). The Content Expert is an active member of the Project Team and is expected to attend meetings, provide feedback and guidance, contribute to the writing of the scientific and analytical protocols, and participate in the preparation of the final manuscript. In addition, they need to be accessible during the conduct of the study to field content-specific questions from the Project Lead and other members of the Project Team. Finally, the Content Expert may be called upon to participate in the Messaging Committee and to serve as a national spokesperson as part of knowledge translation and dissemination activities.

g. Steering Committee Liaison

It is CNODES policy that there be a minimum of two members of the Steering Committee on each Project Team. In the event this minimum is not met when the Project Team is formed, a Steering Committee member is added to the Project Team as a Steering Committee Liaison. The main role of the Steering Committee Liaison is to provide additional leadership and guidance, ensuring that the project is following CNODES protocol and procedures. The Steering Committee Liaison is responsible for reviewing protocols and manuscripts. In addition, this Liaison facilitates communication between the Project Lead and Steering Committee.

h. Representative(s) of the Query Submitter

The Query Submitter has representation on each CNODES Project Team. This representative is there to ensure that the study addresses the information needs of the submitter. CNODES Query Submitter Terms of Reference (which are provided to the Query Submitter Representative by the Project Manager) fully describe their role and responsibilities. This document is provided to the Query Submitter Representative once they are added to the Project Team.

This member is invited to participate in key team meetings and is responsible for bringing all relevant information back to their organization's internal working group, as necessary. Their responsibilities include completing a COI, acting as an advisor to the project team, participating in team meetings up to the development of the final scientific protocol, communicating with the Project Lead and Coordinating Centre, as needed, and maintaining the confidentiality of study materials.

The Query Submitter Representative is to be involved in the initial Project Team meetings. Unless otherwise requested by the Project Lead, the Query Submitter Representative is not asked to provide input or to participate in meetings regarding the analytical protocols. Once the project is complete, the representative is invited to a presentation of the results.

i. CNODES Research Coordinator

The CNODES Research Coordinator plays a crucial role in facilitating the completion of CNODES studies in a timely manner. At the beginning of the study, the Project Lead, Research

Coordinator, and Project Manager develop a study timeline. The Project Manager provides this timeline to the Query Submitter via DSEN.

Throughout the conduct of the study, the Research Coordinator is in constant communication with the Project Lead and assists the Lead in developing timelines and coordinating communication between the Project Team and other standing committees/teams within CNODES. In addition, the Research Coordinator helps to ensure that all CNODES policies and procedures are followed. The Research Coordinator is responsible for ensuring that all sites obtain research ethics board approval, organizes teleconferences and meetings, administers the document sharing system (i.e., Dropbox), and is highly involved in the knowledge translation components of each project (including the 1-page research abstract). The Research Coordinator also provides scientific support, assisting the Project Lead with protocol development, registering the protocol, compiling site-specific results in tables and figures, preparing site-specific data for meta-analysis, etc.

The Research Coordinator ensures that the Representative(s) of the Query Submitter is included in team communications as appropriate.

j. Steering Committee Members Not Sitting on the Project Team

Steering Committee Members who are not members of the Project Team are expected to be involved in the conduct of CNODES studies. They are responsible to ensure that their liaisons are well informed of the roles and responsibilities of the position to which they are committing to at the time of nomination. Steering Committee Members are responsible for seeking updates from the Site Liaisons, providing comments regarding protocols and manuscripts to their Site Liaisons, and ensuring that all ethics and data custodian requirements are met. In addition, it is their responsibility to ensure that Site Liaisons have all resources needed to complete the site-specific analyses (e.g., analyst, data access). All members of the Steering Committee are also required to approve the final version of the scientific protocol and participate in briefings on study results. Steering Committee Members must also review site-specific Phase I and Phase II results with their Site Liaison prior to these results being posted in Dropbox.

In the event that results from their site are not consistent with those of other sites, the Project Lead may request additional analyses and thorough review of analyses conducted to date; the Site Lead is expected to assist the Site Liaison in the thorough investigation of these discrepancies.

3. Communication within a Project Team

Communication within a Project Team is essential. CNODES Project Teams are encouraged to communicate and meet regularly, either by teleconference or in-person (typically at the CNODES semi-annual meetings). Members of the Project Team are expected to notify the Project Lead of any upcoming lack of availability (e.g., vacation) or barriers to project advancement. Furthermore, if not available, it is their responsibility to notify the Project Lead of who will be covering for them during this time (typically, it is the Site Lead).

It is the Project Lead's responsibility to prepare the agendas of all Project Team meetings and to proactively inform their team of the project's development. Minutes from these meetings are taken by the Research Coordinator and finalized by the Project Lead. These minutes are circulated to the Project Team and Coordinating Center following the teleconference or meeting and explicitly list action items emanating from the teleconference or meeting. The CNODES Coordinating Centre provides support for scheduling and ensures the smooth and productive advancement of the study.

a. Teleconferences

All liaisons and analysts are requested to attend Project Team teleconferences. In the event where a Site Liaison is not available, it is recommended that their Site Lead participate in their place.

b. In-Person Meetings

Each Project Team generally has at least one in-person meeting, to which the entire Project Team and analysts working on the project are invited. These in-person Project Team meetings take place during the CNODES semi-annual meetings, though they may also take place via teleconference.

The first is a project launch meeting. This initial meeting is set in order to introduce all team members to one another, review a first draft of the scientific protocol and set feasible timelines. The following topics are usually addressed during this meeting:

- Ethics approval requirements and expected approval dates (for each site)
- Data access requirements and expected time to data access (for each site)
- Timelines
    - Scientific Protocol
    - Analytical Protocol
    - Data Analysis (at the individual site level)
    - Meta-Analysis (by the Methods Liaison)
    - Manuscript Preparation
- Next Meeting(s)

A second in-person meeting that may be held occurs following the completion of the site-specific analyses. This project debriefing, which is attended by the Project Team, is described in section 9 of this Project Guide.

c. Document Sharing

Dropbox is the method used to share and review documents within a Project Team. The Coordinating Centre creates a Dropbox folder for each Project Team and invites all team members to join this project-specific Dropbox folder. Others can be added to the folder upon Site Liaisons' requests and with approval from the Project Lead.

CNODES has established specific Dropbox usage guidelines and provides a copy of these guidelines in each team folder. These guidelines should be consulted at the beginning of each

project. Furthermore, a document containing all team members' contact information, a copy of this project guide, and a description of the query is uploaded to the Dropbox folder at the start of each project.

Site-specific Dropbox folders are also created for each project. The Project Lead, Methods Liaison, Lead Analyst, and site-specific personnel (i.e., Site Liaison and Site Analyst) have access to these folders, which is where the Site Liaison uploads site-specific results. The purpose of these folders is to blind sites to each others' results until the results are approved by the Steering Committee.

d. Email Exchanges

A listserv (or email distribution list) is created at the start of a project that includes all members of the Project Team, analysts working on the project at each site, the Coordinating Centre, and the Coordinator of the Analyst Group. This list is to be used for all project communications, with an email update provided to the team at least once per month. As such, it is essential that the Coordinating Centre be advised of any changes in contact information or study personnel. It is the responsibility of the Site Liaison to keep their Site Lead continuously updated using whatever communications procedures are implemented at that site.

Note: The Query Submitter Representative is not included in the listserv. It is the responsibility of the Research Coordinator to ensure that all relevant communications are sent separately to this individual.

4. Scientific Protocol Development

a. Procedure

The Project Lead is responsible for drafting the scientific protocol. The contents of the scientific protocol are described in detail in the CNODES Protocol Development Guide. Briefly, the scientific protocol should be approximately 5 pages and should contain sufficient detail to allow each site to obtain approval from data custodians and relevant research ethics boards.

The process of drafting the scientific protocol should begin as soon as the Project Lead is approved by the CNODES Steering and COI Committees. While it is the responsibility of the Project Lead to draft the scientific protocol, it should be done as part of a writing team that also includes the Methods Liaison, the Lead Analyst, and another liaison ideally with content expertise (selected by the Project Lead). One of the members of this writing team must be a member of the Steering Committee. The early involvement of the Methods Liaison is crucial to ensure that the proposed methodological approach is both rigorous and one that the Project Team has the expertise to conduct.

The Project Lead requests from the Site Liaison a list of relevant drug formulary restrictions that are in place in their jurisdiction to help inform the development of the scientific protocol.

Once the first draft of the scientific protocol is completed, it is circulated to the Project Team for comments via Dropbox; please refer to the CNODES Dropbox etiquette document. At the time of circulation, a Project Team meeting (teleconference or in-person) should be scheduled, allowing the Project Team approximately 1 week to review the first draft of the scientific protocol. During this time, the Site Liaison should solicit feedback from CNODES members at their site, including their Site Lead and the analyst who is working on the project. During the teleconference, members of the Project Team should actively participate in discussion, with site analysts present to provide support and address analytical issues that arise.

Following the teleconference and with the assistance of the Methods Liaison, the Project Lead revises the scientific protocol based on comments received from the Project Team and members of the Steering Committee. The revised version of the scientific protocol is then posted in Dropbox for additional comments by the Project Team. Depending on the extent of revisions, it may be necessary to hold an additional teleconference at this time. This process can be repeated until consensus is achieved regarding the proposed study design, balancing the need for timely protocol development with the need to minimize future protocol modifications.

If the Project Lead is not a Steering Committee member, it is strongly encouraged to have their Site Lead review the revised protocol before circulation.

When revising the scientific protocol, the Project Lead may request that one or more sites conduct preliminary analyses to assess the feasibility of the proposed methodological approach. This feasibility assessment is important for the early identification of important methodological barriers (e.g., limited statistical power). Some sites have access to subsets of databases (e.g., Manitoba) or prompt access (e.g., Ontario) that allow for quick feasibility assessment.

Following revisions by the Project Team, the scientific protocol is circulated to the Steering Committee for their review and approval via the CNODES Project Manager (using the Steering Committee folder of Dropbox); substantive comments should be minimal since the Project Liaison should have discussed it with the participating Site Leads during the development of the scientific protocol. The Steering Committee is given a maximum of 1 week for this review. Approval is required by all members of the Steering Committee, including those whose sites are not participating in the study.

Once the scientific protocol is finalized, the Project Lead places a copy of the final protocol in the Project Team folder in Dropbox. The Project Lead is also required to notify the team that the final version is available, and this version is to be used to obtain ethics and data custodian approval. Please note that, depending on the results of phase I of the analytical protocol (described below), the scientific protocol may need to be updated, with amendments and modifications clearly described in an amendments appendix, with corresponding changes in the main document clearly indicated (e.g., using blue font).

Following the completion of the scientific protocol, the Project Lead is expected to provide the Project Team with a list of upcoming deadlines.

b. Ethics

Research ethics approval is required from all CNODES sites participating in a given project.

Following the completion of the scientific protocol, each Project Liaison is responsible for obtaining research ethics approval from their institution.

Once obtained, the Project Liaison emails the Research Ethics Board approval letter (as well as any annual renewal) to the CNODES Coordinating Center.

Research ethics approval is typically valid for one calendar year. It is the responsibility of each Project Liaison to maintain research ethics approval until the publication of the manuscript or report to ensure that any additional or sensitivity analyses requested by journals can be completed in a timely manner.

c. Data Access

Each site is also responsible to obtain approval/access from their respective data custodians using the final scientific protocol. The Site Liaison should inform the Project Lead and Research Coordinator of the anticipated timelines with respect to data access and provide subsequent updates to these timelines as needed.

The procedures used to obtain this approval/access vary site-to-site; Project Liaisons must discuss procedures with their Site Leads to ensure that all requirements are met.

Once obtained, the Project Liaisons are responsible for informing the Project Lead via email.

5. Public Registration of CNODES Protocols

CNODES is committed to transparency in the conduct of its studies. Consequently, protocols for CNODES projects conducted in response to a DSEN query are publicly registered via www.clinicaltrials.gov.

Following the completion of the Phase I of the analytical protocol (described below), the Research Coordinator completes the CNODES Protocol Registration Form. This form, available from the CNODES Coordinating Center, includes the data elements requested by www.clinicaltrials.gov. This form is then reviewed by the Project Lead and, following any required revisions, the CNODES Publications Committee (or its designate).

Once approval of the scientific protocol has been obtained from all relevant data custodians, the CNODES Coordinating Center uploads the contents of the Registration Form to www.clinicaltrials.gov using the CNODES user name and password. Information is uploaded via the Coordinating Center to ensure that all protocols are registered to CNODES rather than the individual Project Leads.

Registration only includes information contained in the final scientific protocol sent to data custodians. This process ensures that it is only the proposed protocol that is registered rather than a subsequent version that has been influenced by study results, ensuring the transparency of our work.

In addition to the Public Registration of CNODES protocols, scientific protocols are simultaneously uploaded as PDF documents to the CNODES website (www.cnodes.ca). Given the public posting of scientific protocols, their formatting may be modified by the Coordinating Center prior to posting to ensure consistency.

6. Analytical Protocol Development

Following the completion of the scientific protocol, the analytical protocol is developed. This document is the responsibility of the Project Lead. The Project Lead, Methods Liaison, Lead Analyst, and Content Area Expert agree at the beginning of the development of this document who is responsible for each component of the analytical protocol. Typically, the Project Lead and Content Area Expert draft sections that require substantive knowledge, and the Methods Liaison and Lead Analyst draft the more analytical sections. The draft of the analytical protocol is reviewed by all 4 of these team members before being circulated to the rest of the Project Team.

The list of required DINs is provided by the Manitoba site.

The analytical protocol follows the scientific protocol but is written in such technical detail that it allows for the scientific protocol to be implemented in an identical manner (except for instances where site-specific protocol adaptations are required due to, for example, data availability) at each of the participating sites.

Analytical protocols must be written following the CNODES template; this template is available from the CNODES Coordinating Center.

Once drafted, the analytical protocol is circulated via Dropbox for review by the Project Team. During this review, it is important that Site Liaisons liaise with members at their respective sites. In addition to their own comments, the Site Liaisons should include comments and feedback from their analysts and Site Leads. The Project Team is typically given one week to review the draft. A teleconference is then held to discuss comments received and required amendments. This process is then repeated until a consensus is reached.

To maintain continuous communication within the Project Team, regular teleconferences are scheduled by the Project Lead via the Coordinating Center. Two to three teleconferences should be scheduled in advance to ensure maximal availability of Project Team members.

To minimize the number of protocol amendments that need to be implemented during the analysis (see below), it is recommended that the analytical protocol be developed using a

modular or multi-phase approach. However, despite the use of this approach, some amendments are inevitable. These amendments and modifications must be clearly described in an amendments appendices to Phase I and Phase II of the analytical protocol, with corresponding changes in the main document clearly indicated (e.g., using blue font).

Phase I:
In this stage, sites are typically asked to provide a study flow diagram describing the derivation of the study cohort, basic descriptive information (e.g., age categories, sex, calendar year of cohort entry, drug (or disease) that defined cohort entry), and overall incidence rate of the primary outcome in the cohort (no outcome analyses by exposure status are to be conducted in Phase I). It may also be useful to examine major confounders typically included in CNODES studies (e.g., number of prescriptions in the last year, number of physician visits in the last year) and follow-up times in groups being compared. In the initial analyses described in Phase I of analytical protocol, it may also be useful to carry out a drug utilization study. For example, it may be helpful to document the number of prescriptions per quarter, the number of patients switching from one drug class to another, the distribution of doses and durations, etc. If relevant, sites may also be asked to calculate high-dimensional propensity scores, apply trimming criteria, and provide a descriptive table of the trimmed cohort for the groups being compared as part of this initial step. Other descriptive analyses may also be requested. This information is used to ensure that the initial components of the study protocol are implemented consistently across sites and help explain heterogeneity observed across sites when conducting Phase II analyses.

Note: Phase I results are reviewed by the Project Team but the Steering Committee is not required to sign off on Phase I results. However, individual Site Leads are expected to review the results from their site with their Site Liaison. In addition, there is no need to blind Site Liaisons from sites that have not yet completed Phase I results when reviewing these results with the Project Team as there are no measures of association; the discussion of these results may result in protocol changes, and all members of the team should be present for such discussions.

Phase II:
Once data from Phase I of the analytical protocol are reviewed by the Project Team, site-specific corrections are made, and the protocol may be revised to ensure study feasibility. Following approval of phase I results by the Project Team, the remaining steps in the analytical protocol (phase II) are carried out (primarily running the outcome models and sensitivity analyses).

7. Site-Specific Analyses

Site-specific analyses are conducted by each site's analyst under the direct supervision of their Site Liaison. Site Leads must review all results with their Site Liaison prior to these results being posted in Dropbox.

Analysts begin the implementation of the protocol in their database following the completion of phase I of the analytical protocol and approval from data custodians (if required at that site). There is no need to wait for all sites to have data access to begin phase I. Some sites may begin cohort construction prior to the availability of the first phase of the analytical protocol; consequently, the scientific protocol should include sufficient detail (particularly regarding study population and cohort entry) to commence analyses, acknowledging that some changes between the two are inevitable.

Although the analytical protocol is intended to be implemented in an identical manner in each database, some adaptations from this protocol will be required due to data availability, data structure differences, etc. These adaptations are decided upon and implemented by the Site Liaison and Site Analyst, though the Project Lead should be consulted for major adaptations. It is the responsibility of the analyst to record all site-specific protocol adaptations using the form provided by the Research Coordinator. Separate forms may be used for Phases I and II, with the contents of the form mirroring the sections of the corresponding analytical protocols. These forms are uploaded to Dropbox when submitting Phase I and Phase II results using the Excel workbooks provided by the Project Lead and/or Research Coordinator.

Following the completion of the study, the Project Lead must provide the CNODES Coordinating Center with the final protocol, including a complete list of site-specific protocol adaptations.

Questions arise during the conduct of site-specific analyses. Questions of a substantive or project specific nature should be addressed to the Project Lead and Methods Liaison, usually through the project listserv, since these may be relevant to other sites. Otherwise, narrowly site-specific questions may be addressed directly to the Project Lead and Methods Liaison. Given the frequency of questions that arise during the conduct of site-specific analyses, it is essential that the Project Lead, Methods Liaison, and Lead Analyst be readily available during this period to ensure the timely completion of all analyses. It is helpful for the Project Lead, Methods Liaison, and Lead Analyst to keep a list of questions and answers that arise to allow the Project Lead to include them in the "Protocol Clarification" appendix in an updated version of the analytical protocol. New versions of the protocol are shared via Dropbox, with an email sent from the Project Lead to the Project Team alerting them to the availability of this revised document.

Purely technical questions (i.e., programming) may be addressed directly to the project's Lead Analyst via the Project Team listserv. If the Lead Analyst believes that it is pertinent to the larger group of CNODES analysts, they may forward it to the Analyst Group listserv (a separate group that includes all CNODES analysts and not just those working on a particular project). This process ensures that the same question is not sent to the Lead Analyst multiple times while also contributing to capacity building across sites. For this reason, all analysts must be part of

both the Project Team listserv and the analyst group listserv during the conduct of the study (i.e., from Project Team formation to publication of the manuscript).

As a result of questions asked and issues identified, protocol amendments are required. These amendments should be communicated to the Project Team by the Project Lead in two ways: 1) they should be described in an email sent to the project listserv; 2) they should be listed in the "Protocol Amendments". If major (or a large number of minor/moderate) amendments are needed, they should be listed in both the appendix and incorporated into the body of the protocol itself (with changes clearly indicated).

Analysts must be given at least one week between the last amendment and the deadline to submit results to allow them adequate time to conduct the analyses and perform quality assurance.

The Research Coordinator and Project Lead create Excel files to be completed by each site with their site-specific analyses. These files are reviewed by the Lead Analyst and Methods Liaison prior to their posting in Dropbox. **These Excel files should not be modified in any way to ensure that all sites provide results in identical formats.** For this reason, the Excel Workbooks should be locked by the Coordinating Center. These Excel files should be uploaded with the Site's initials added to the file name for ease of identification.

The Coordinating Center creates a site-specific Dropbox folder for each project. Only the Project Lead, Methods Liaison, Site Liaison, Site Analyst, and Coordinating Center have access to this folder to maintain the blinding of all sites to the site-specific results of the other sites. Results are retrieved from these Dropbox folders for the meta-analysis of site-specific results. Final results should be reviewed by the Site Analyst, Site Liaison, and Site Lead prior to uploading.

Due to small cell reporting rules instituted at each site, it may not be possible for individual sites to report small numbers with their site-specific results. In most cases, the exact number that is suppressed is not needed. Consequently, the midpoint of the range of suppressed numbers may be used (i.e., if sites cannot report <5, a value of 3 is assumed). If the actual true sum of suppressed cells is needed, a serial data entry procedure that avoids disclosure of small cells will be implemented.

The presentation of meta-analysis results to the Steering Committee (described below) may take place as either a teleconference or in person at one of our semi-annual meetings (typically one in the fall and one in the spring). These meetings often therefore serve as internal deadlines for the completion of site-specific analyses and their meta-analysis; these deadlines should be considered when developing project timelines.

8. Meta-Analysis of Site-Specific Estimates

Following the completion of site-specific analyses, the Research Coordinator creates an Excel file that contains site-specific estimates that are to be included in the meta-analysis. This Excel file should contain event counts, adjusted point estimates, and their confidence intervals. In addition, it should be organized such that there is only one data point per cell (e.g., lower and upper limits of confidence intervals need to be in separate cells), with each analysis clearly labeled.

In cases where the Methods Liaison is unable to perform the meta-analysis, the Methods Liaison must alert the Project Lead and Methods Team Lead to this during protocol development. In such cases, the Excel file is provided to the Methods Team Lead, who arranges for the meta-analysis to be performed.

Site-specific estimates are pooled across sites using standard meta-analytic techniques, and outlier identification methods may be used as part of quality assurance processes.

To ensure that the meta-analyst has sufficient time to conduct and verify the analyses, the Project Lead must provide them with site-specific estimates at least one week before a scheduled debriefing session or presentation.

It is possible that there are unexpected delays that arise that prevent a site from completing analyses in a timely manner (e.g., data access issues). In such cases, the Project Team and Steering Committee will consider the most appropriate course of action (e.g., wait for missing data, exclude the site with missing data, etc.) taking into account the sample size of remaining sites, expected timelines, and appropriate consideration of results available from other sites.

Finally, if heterogeneity in site-specific results exists and appears important, on the advice of the Project Lead and Methods Liaison, outlier analyses may be required to determine if additional quality assurance processes should be conducted at any particular site (e.g., running one site's code on another site's data). The Site Liaison is expected to thoroughly investigate potential causes of heterogeneity, with the involvement of the Site Lead.

9. Project Debriefing

The project debriefing consists of two components: the Steering Committee debriefing and the Project Team debriefing. These sessions can be either in-person meetings or conducted via conference call. The dates of these debriefing sessions often serve as unofficial deadlines for the completion of site-specific analyses and the meta-analysis of site-specific results; consequently, they should be considered when developing project timelines.

a. Steering Committee

Following the completion of the meta-analysis, the Project Lead and Methods Liaison are invited to attend a portion of a Steering Committee meeting/teleconference to debrief regarding the project. Quorum is required and includes a minimum of 8 members of the Steering Committee and includes at least 1 member of the CNODES Executive Committee, 1

member of the Methods Team, and leads from at least 4 different sites. Importantly, members of the Steering Committee whose sites have not yet submitted their site-specific results cannot participate in this session and should not be sent the slide deck with preliminary results in order to maintain blinding.

This session typically begins with a brief presentation of the background, rationale, and objectives of the study, followed by the presentation of site-specific and meta-analytic results. A question and answer session is also held to discuss challenges faced, potential solutions, etc. Following the discussion of study results, the Steering Committee then decides if the site-specific and meta-analytic results can be released to the Project Team (minus any team members from sites who have not submitted their results) or if additional analyses are required. The Steering Committee may also suggest that additional sensitivity analyses be conducted following the unblinding of the Project Team. The results presented to the Steering Committee should not be presented on CNODES slides to ensure that they are not portrayed as final results. To facilitate the discussion of results, all slides should be numbered. A copy of all debriefing materials, including PowerPoint presentations, is to be provided to the Coordinating Center for record keeping purposes.

b. Project Team

The primary purpose of this session is to obtain feedback from the Project Team, including both analysts and liaisons. This session is attended by the Project Team, though members of the Steering Committee and observers can request or may be asked to attend. Minutes are taken by the Research Coordinator. The session can be held either in person or via teleconference.

The majority of the Project Team debriefing is devoted to the discussion of debriefing questions; the Project Lead should circulate these questions to the Project Team approximately one week before the session. These questions typically address areas for improvement, challenges faced, feasibility of timelines, suggestions to improve process, and next steps (e.g., manuscript preparation, additional analyses). For each question, the Project Lead provides a representative from each site (either analyst or liaison, depending on the question) the opportunity to provide feedback. Given the time constraints, only 4-6 questions can be addressed in the debriefing session; answers to these questions as well as answers to additional questions are to be provided to the Project Lead and Coordinating Center before or after the session via email. Answers are shared with members of the Project Team. In addition, these answers are sent to the Coordinating Center and later reviewed by the Policies and Procedures Committee. They will be used to improve CNODES procedures and inform future versions of this Project Guide. Furthermore, to facilitate the debriefing, Project Team members at each site should discuss answers to the debriefing questions prior to the session. Minutes from this session and answers to debriefing questions are provided to the Coordinating Center following the Project Team debriefing.

The Project Team debriefing may also include the presentation of the site-specific and meta-analytic results. This presentation only occurs once the Steering Committee has accepted the results and agreed to the unblinding of participating sites. As with the Steering Committee

debriefing, members of sites who have not yet submitted their site-specific results cannot participate in this component of the debriefing.

c. Query Submitter

Following the Project Team Debriefing, the Project Lead chairs a teleconference with DSEN and the Query Submitter, which is arranged by the Coordinating Center. This teleconference typically consists of a 15-30 minute PowerPoint presentation by the Project Lead, followed by a question and answer period. A copy of the slides, based on those presented to the Steering Committee but updated per feedback received, is reviewed by the CNODES Publications Committee prior to being circulated to DSEN. As with all CNODES presentations, the CNODES slide template is used.

Note: Interim briefings may be held if CNODES is able to provide meaningful information before all analyses are final.

10. Knowledge Translation and Dissemination

a. Final Reports to Query Submitter

As per DSEN's KT guidelines (http://www.cihr-irsc.gc.ca/e/49134.html), CNODES is expected to provide 1-, 3-, and 25-page reports to the Query Submitter. The 1-page report consists of a DSEN research abstract (described below). The 3-page report consists of the slide desk used for the final debriefing of the Query Submitter. Finally, the detailed (roughly 25-page) final report is a description of the information provided during the Query Submitter Debriefing.

The detailed final report is prepared by the Project Lead (or Lead Author of the manuscript), with the objective of providing the submitter with a rapid answer to their query. Although manuscripts satisfy the reporting requirements, reports are created to avoid any delays related to the development and finalization of the academic manuscript. The final report summarizes the rationale for the study, methods used, results, and conclusions.

Once drafted, the final report is reviewed by the Publications Committee and circulated confidentially to the Query Submitter (via DSEN). CNODES uses an integrated Knowledge Translation approach, where the decision maker (i.e., the Query Submitter) is a partner and an integrated member of the research team, and thus data custodian approval is not needed prior to the submission of this confidential report. Nonetheless, a copy is provided to the relevant data custodians for their information only.

All material provided to the Query Submitter is labeled as "Confidential – Do Not Circulate" as to not infringe of the ability to publish study results in an academic journal and to ensure that all data custodians have the opportunity to approve results prior to their public release.

The final report and teleconference must take place prior to the submission of the full manuscript for publication and the public presentation of results (e.g., conference presentation).

b. DSEN 1-Page Research Abstract

For each study, a 1-page research abstract is written by the Project Lead and/or the Research Coordinator following the DSEN template at the time of manuscript submission. Once drafted, it is reviewed by Project Lead (if necessary), the KT Team Lead, and then the CNODES Publications Committee. This 1-pager is written at a level appropriate for the Query Submitter. Once finalized, it is provided to the Project Manager, who emails it to DSEN for posting on their website at the time of manuscript publication to respect journal embargo policies.

c. Manuscript Preparation

The manuscript preparation process is described in detail in the CNODES Publications Policy. The Coordinating Centre provides the Project Lead with a copy of this policy following project debriefing. Additional steps regarding manuscript preparation are described below.

A manuscript writing committee is put together by Project Lead, which typically consists of 3-4 individuals, including the Project Lead, Methods Liaison, and the Content Expert. The writing committee should include at least one Steering Committee member.

It is essential that the Steering Committee debriefing occur (and the approval of un-blinding be given) before circulating the manuscript to members of the writing team. In addition, the conclusions of the manuscript must be consistent with those presented to and approved by the Steering Committee.

Once the manuscript is submitted, the Coordinating Centre contacts the KT Team Lead to begin the development of the messaging strategy and material. This process is described in detail in the KT Messaging Procedures Document.

Once the manuscript is *in press*, the Coordinating Centre informs DSEN and the CNODES KT Team Lead of the anticipated publication date.

d. Data Custodians and Provincial Agencies

It is the responsibility of the Site Liaison and Site Lead to ensure that all reporting requirements to data custodians and provincial agencies are met.

The timelines required for manuscript and abstract review by the individual data custodians are provided in Appendix 1 to the CNODES Publications Policy. These timelines should be consulted by the Project Lead when developing the project timeline and deadlines.

e. Open Access Publication

CNODES will meet (or exceed) CIHR requirements regarding open access publications, which require that the manuscript be freely available within 12 months of publication (http://www.cihr-irsc.gc.ca/e/32005.html).

For all CNODES publications written directly in response to a DSEN query and where immediate open access publication is possible, it is CNODES policy to cover the costs of open access publication.

For CNODES publications not written directly in response to a DSEN query (e.g., secondary papers, methods papers) and those published in journals that do not allow immediate open access publication, it is CNODES policy to deposit the manuscript in an open-access repository, such as PubMed Central Canada (http://pubmedcentralcanada.ca/pmcc/). It is the responsibility of the Lead Author (with assistance from the Research Coordinator) to deposit the manuscript such that CNODES fulfills the CIHR policy, while respecting the copyright agreement with the publishing journal. Authors should consult journal publishers' policies regarding open access publication.

f. Messaging

Once the manuscript is submitted, the Coordinating Centre contacts the KT Team Lead to begin the development of the KT strategy for the project. This process includes contacting members of the KT team to develop a list of key stakeholders that would be interested in the results of this particular project, the identification of KT activities most appropriate for each stakeholder, and the conduct of background research needed for the development and implementation of the KT strategy.

A detailed description of the procedures used to develop and implement the project-specific KT strategy is found in the CNODES KT Messaging Procedures document.

11. Timelines for CNODES Projects Addressing a DSEN Query

Although each project is different, all CNODES projects that address a DSEN query should generally follow the recommended timeline below. This timeline, which delineates the lifecycle of these projects, should be used to gauge progress and plan next steps and aligns with DSEN guidelines (http://www.cihr-irsc.gc.ca/e/documents/dsen_kt_guidance_doc-en.pdf).

Note: Bold indicates benchmarks provided to DSEN and Query Submitters for CNODES project lifecycle by the CNODES Project Manager; other steps are for internal guidance.

Time 0	• **DSEN informs CNODES that they can move forward with the accepted query**
Weeks 1-4	• Nominations for Project Team members (Project Lead, liaisons, and analysts) submitted • Nomination of Query Submitter Representative requested by Project Manager from Query Submitter • COI forms completed by Project Lead, liaisons, Lead Analyst, and Query Submitter Representative

Weeks 1-4	• Project Lead starts drafting scientific protocol in consultation with Methods Liaison and Lead Analyst
Week 4	• **Project Team composition finalized** • **Composition of team circulated to all team members, including Query Submitter Representative**
Week 8	• **First draft of scientific protocol circulated by Project Lead to Project Team** • Project Team invited to Dropbox
Weeks 9-17	• Scientific protocol reviewed by Project Team • Team meeting to discuss scientific protocol • Scientific protocol finalized by Project Lead with assistance from Methods Liaison and Lead Analyst
Weeks 18-19	• Scientific protocol reviewed and approved by Steering Committee • Comments from Steering Committee incorporated by Project Lead
Week 20	• Approved scientific protocol circulated by Project Lead to Project Team • Submission of scientific protocol to data custodians and REBs by Site Liaisons • Site Liaisons provide Project Lead with estimated time to data access
Week 20	• **Approved scientific protocol circulated to Query Submitter Representative, who is notified that the analytical phase of the study begins**
Weeks 20-22	• First draft of phase I of analytical protocol written by Project Lead, Methods Liaison, and Lead Analyst • First draft of phase I of analytical protocol circulated by Project Lead to Project Team
Weeks 23-25	• Phase I of analytical protocol reviewed by Project Team • Team meeting to discuss phase I of analytical protocol • Phase I of analytical protocol revised by Project Lead, Methods Liaison, and Lead Analyst
Weeks 25	• **Query Submitter Representative notified that phase I analyses beginning**
Weeks 26-29	• Phase I of analytical protocol implemented by Project Team • Site-specific results vetted by Site Lead

	• Phase I results discussed by Project Team • Phase I of analytical protocol revised and re-implemented as needed
Week 29	• **Query Submitter Representative notified that phase I analyses complete and phase II beginning** • **Query Submitter Representative updated on data access status at participating sites**
Weeks 30-31	• Public registration of scientific protocol
Weeks 30-32	• Phase II of analytical protocol drafted by Project Lead, Methods Liaison, and Lead Analyst
Weeks 33-34	• Phase II of analytical protocol reviewed by Project Team
Week 35	• Phase II of analytical protocol revised by Project Lead, Methods Liaison, and Lead Analyst
Week 36	• **Query Submitter Representative notified that phase II analyses beginning**
Weeks 36-42	• Phase II of analytical protocol implemented by Project Team • Site-specific results vetted by Site Lead • Site-specific protocol amendments form completed by Site Liaisons
Weeks 43-46	• Meta-analysis (when applicable), outlier assessment, and quality assurance activities
Weeks 47-49	• Presentation of results to Steering Committee • Presentation of results to Project Team
Week 50-56	• Final report to Query Submitter drafted by Project Lead • Final report to Query Submitter reviewed by Project Team • Final report to Query Submitter revised by Project Lead • Final report to Query Submitter reviewed by Publications Committee
Week 52	• **Debriefing teleconference held with Query Submitter**
Week 56	• **Final report to Query Submitter provided to data custodians and Query Submitter (via DSEN)**

Note: While this timeline is based on previous experience addressing DSEN queries, these timeframes should serve as guides, with every effort made to shorten the project length where possible.

Note: The above timeline does not include the production of scientific manuscripts written after the CNODES report to the Query Submitter and corresponding knowledge translation activities.