Draft guidance on decentralized clinical trials

This guidance document is being distributed for comment purposes only.

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Health Canada Santé Canada

Canada

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the department to adequately assess the safety, efficacy or quality of a drug or clinical trial. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice, the Clinical Trials Regulations (regulations) under section 30 of the *Food and Drugs Act* (FDA) and the relevant sections of other applicable guidance documents.

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Purpose

This guidance outlines regulatory considerations for conducting decentralized clinical trials in Canada. These considerations are supported by Part C, Division 5 of the Food and Drug Regulations (regulations) and the International Council for Harmonization Guideline for Good Clinical Practice (ICH E6).

In decentralized clinical trials, some or all trial-related activities are conducted at locations other than traditional trial centres with the help of digital health technologies and virtual methods. Decentralized elements can help reduce the travel burden for participants and also make clinical trials more accessible and diverse.

Health Canada is currently modernizing how clinical trials are regulated. This modernization initiative is intended to better accommodate new trial types and designs.

Learn more about the clinical trials modernization initiative.

This guidance is an interim measure to support decentralized clinical trials under Part C, Division 5 of the regulations. Once the modernized regulatory framework is in force, we will update this guidance to reflect the new regulations.

Scope and application

This guidance applies to any party involved in conducting clinical trials in humans in Canada. This includes:

- sponsors
- investigators
- other third parties such as local health care providers, local clinical laboratories or service providers

This guidance concerns the following clinical trials involving drugs that are conducted in humans in Canada:

- phases I to IV
- clinical trials involving pharmaceuticals, biologics and radiopharmaceuticals for human use

This guidance does **not** apply to:

- clinical trials involving medical devices
- clinical trials involving natural health products
- foods for special dietary purposes

The considerations listed in this guidance apply specifically to decentralized clinical trial activities. For a complete understanding of regulatory requirements for clinical trials, consult:

- Clinical trial sponsors: Clinical trial applications
- Good clinical practices (GCP) for drugs for clinical trials involving human subjects (GUI-0100)

Policy statements

Decentralized clinical trials consist of visits and activities that are conducted outside of traditional clinical trial centres, bringing research closer to participants. They can:

- improve access to clinical trials and potentially promising new therapies for people across Canada
- help connect a greater diversity of participants to research led from urban centres

They also allow researchers and other health care providers in remote areas to better connect to and participate in pan-Canadian research efforts, without requiring them to be co-located geographically.

Planning and conducting a decentralized clinical trial may involve other considerations, but the regulatory requirements are the same as any other clinical trial.

As part of their clinical trial applications (CTA), sponsors must demonstrate in documentation that the inclusion of decentralized elements or activities are not against the best interest of participants.

Sponsors must also demonstrate that:

- participants are told about the risks and benefits of participating in the trial
- participant risk is minimized and safety will be appropriately monitored **and**
- the objectives of the study can be achieved

Sponsors must identify the decentralization-related risks and manage those risks according to the regulations and ICH E6 guidelines. Managing the risks requires well-coordinated trial monitoring and oversight by all parties involved in conducting the clinical trial. Risk mitigation strategies can be built into various aspects of the trial, such as protocol design, contractual agreements and the informed consent process. They can also be outlined in other trial-related documentation that defines and records the roles and responsibilities of everyone involved in the trial.

Decentralized clinical trials should:

- be operationally feasible and implemented with necessary safeguards and ethical considerations that are in proportion to the risks to participants
- avoid unnecessary burden on participants, investigators and trial-related personnel or other third parties involved in decentralized elements
    - for example, offer flexible options so participants may opt in or out of decentralized elements, based on individual needs that may change over the course of the trial

Decentralization can involve a qualified investigator (QI) at a main location of a clinical trial site, who delegates trial-related activities to personnel or third parties in other physical locations. Regardless of geography, all locations where trial-related activities occur under the supervision of a QI are considered part of a single clinical trial site. A “clinical trial site” refers collectively to the main location and other locations.

- The main location associated with the QI must be listed on the Clinical Trial Site Information (CTSI) form submitted to Health Canada and must have research ethics board (REB) approval before the trial begins.
- Health Canada does not require separate CTSI forms or REB approvals for other locations where delegated activities occur, provided they are overseen by the QI and follow the approved protocol.

Background

Decentralized elements may involve using validated digital health technologies and community-based health care resources, such as:

- wearable sensors or medical devices to monitor and measure outcomes
- internet-based tools for collecting and managing electronic participant-reported outcomes
- telehealth platforms, such as online portals and videoconferences with investigators
- direct-to-home shipping of investigational drugs, including the use of local pharmacies for investigational drugs with specific storage and handling conditions
- at-home visits by trial personnel or follow-up visits with local health care providers who may be known to the participants
- testing and imaging, such as a blood test, at local clinical laboratories

Decentralized clinical trials also make it possible for community-based health care professionals to participate in research activities. Partnering with a traditional clinical trial site could also help them gain access to more clinical trials and potentially beneficial novel treatments.

Decentralization is very important for clinical trials that face challenges with recruiting sufficiently large, geographically and culturally diverse participant group, such as rare disease trials. It can also improve the ability to recruit and retain a more representative participant group, which can lead to stronger and more general evidence or results.

Conducting geographically dispersed trial activities under a single clinical trial site can also reduce logistical or administrative burdens associated with operating multiple sites or coordinating participant visits across several locations.

Decentralized clinical trials can reduce the need for participants to travel to a traditional clinical trial site, allowing for more efficient participation. And for those who cannot travel due to family, work, geography or circumstance, a decentralized option means they can connect to research efforts and have access to novel treatments.

Design considerations for decentralized clinical trials

Sponsors may use several strategies to:

- increase trial efficiency
- reduce participant burden
- appropriately monitor their safety

For example, in a large cohort or a national trial, sponsors could establish multiple clinical trial sites under a single clinical trial application (a multi-site trial). Each clinical trial site would require its own CTSI form. Table 1 lists things to consider when designing a decentralized clinical trial.

Table 1: Design items to consider for decentralized clinical trials

Consideration	Single-site with decentralized elements	Multi-site
Trial suitability	Suited for investigational products with an established safety profile or where complex initial assessments can be done centrally with follow-ups at home	Suited for complex trials, those needing large cohorts or where in-person site-specific interactions are required
QI oversight	Single QI is responsible for overseeing and monitoring trial activities at all locations	A separate QI is responsible for each of the clinical trial sites, including any decentralized elements associated with that site
Operational model	Main location, with remote activities at other locations to facilitate trial activities	Distributed operations across multiple independent sites, under a single study protocol
Administrative burden related to REBs	Approval only needed from the REB related to the main location	REB approval is required for each of the clinical trial sites

Consideration	Single-site with decentralized elements	Multi-site
Interprovincial considerations	Decentralized elements that cross provincial jurisdictions may introduce additional considerations related to applicable provincial regulations	Decentralized elements that cross provincial jurisdictions may introduce additional considerations related to applicable provincial regulations
Patient reach	Broad geographic reach, up to a point Participant-centric by reducing travel burden	Broad geographic reach due to having sites in different areas

Multi-site trials

For multi-site trials, there must be a QI for each clinical trial site. The QI must maintain their own delegation log and documentation to demonstrate compliance with Division 5 of the regulations and the applicable GCP requirements. For a large sample size or pan-Canadian clinical trial, a multi-site design may help overcome provincial or territorial legislative requirements for sharing participant data or around institutional REB approvals.

QIs and sponsors may also use decentralized elements in multi-site trials to reduce participant burden and involve local health care networks (taking into account their capacity to participate). When decentralizing activities in a multi-site trial, sponsors should ensure that trial-related activities delegated from each QI's main location are within the scope of that site's REB approval and supervised by the site-specific QI.

Research ethics boards

As per the regulations, each clinical trial site must receive REB approval before a trial can begin at that site.

By decentralizing trial-related activities to trial-related personnel or other third parties in other locations, sponsors and QIs can conduct REB-approved trial activities across a wider geographic area. While Health Canada doesn't require additional REB approvals, sponsors may need to obtain additional approvals, permissions or meet community-specific requirements to gain access to specific locations or populations.

For multi-site trials where Health Canada requires each clinical trial site to obtain a REB approval, sponsors should consider using streamlined REB review systems.

Find information on multi-jurisdictional research under the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

In some cases, an institution may allow its REB to rely on an external REB's review to decide if a study is ethically acceptable. This may be especially true if the REBs are recognized members of a streamlined ethics review network or have formalized cross-institutional agreements.

Several initiatives and organizations have facilitated more streamlined ethics review systems in Canada:

- CanReview, Canada's single research ethics review system
- REB Exchange Alberta (REBX)
- Clinical Trials Ontario's streamlined ethical review
- CATALIS, Québec's fast track evaluation service
- Research improvements through harmonization in Manitoba (RITHIM)
- Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research

Considerations for coordinating decentralized clinical trials

When decentralizing activities from the QI's main location to other locations, sponsors should minimize the risk to participants and safeguard the integrity and security of trial data.

QIs may delegate trial activities to individuals or organizations located outside their main location. These delegated activities can range from highly specialized trial-related procedures requiring specific equipment or assessments to non-trial-specific activities such as routine blood work or imaging.

When deciding to decentralize trial activities, QIs and sponsors should consider:

- the level of risk posed by the investigational drug, including the extent to which its safety profile has been established
- requirements for specialized preparation, administration and evaluation procedures or equipment
- study-specific training needs for delegated third parties, such as delegated trial personnel, local health care providers or clinical laboratories
- how to consistently and appropriately record delegated third parties in trial-related documentation (for example, delegation log or supervision plans) without creating unnecessary administrative burden
- how to communicate between locations, trial-related personnel and participants, including providing information critical to participant safety such as test results
- how to transport and store investigational products, including security and control of investigational products, especially those classified as controlled drugs

Digital health technologies should be validated for their intended use and demonstrate compliance with ICH E6, for example, by:

- tracing any changes and updates, such as source, date and content (audit trail)
- backing up at regular intervals
- having security measures in place to protect against data corruption, whether through accidental deletion, equipment failures, material deterioration or other hardware and software problems
- controlling access to appropriate individuals (such as through use of passwords)

- planning for future accessibility (in light of changes over time in technology, personnel or third-party contractors)
- allowing immediate access to records for inspection

Agreements (or contracts) can help all parties who conduct trial activities know their roles, responsibilities and liabilities. They can also help protect the safety of trial participants.

Written agreements should clearly set out:

- individual roles and responsibilities (who conducts certain activities and where)
- required qualifications, through education, training and experience, of personnel who conduct trial activities
- how specific trial activities will be conducted and monitored for compliance to the protocol
- professional liability among sponsors, QIs, sub-investigators and delegated third parties, including local health care providers
- procedures for safety monitoring and timely reporting of adverse events
- indemnity coverage for participants
- other considerations related to activities with specific groups, communities and Indigenous communities

Agreements that are clearly written and set out the division of responsibilities can help trial personnel, service providers and local health care providers comply with applicable laws, regulations and professional standards.

Records of agreements (paper or electronic) must be available or accessible from the main location (associated with the QI) of the clinical trial site. They may be reviewed during an inspection to ensure that all:

- relevant activities are covered
- relevant parties are mentioned and audited
- agreements are complete

As per subsection C.05.012(4) of the regulations, records of contractual agreements must be maintained for 15 years.

Submitting a clinical trial application

A CTA is not required for clinical trials involving marketed drugs where the investigation is to be conducted within the parameters of the notice of compliance (NOC) or drug information number (DIN) (phase IV trials).

As part of their CTA, sponsors must provide information to show that the:

- trial minimizes risk to participants
- participants will be monitored appropriately throughout the trial **and**
- objectives of the trial can be achieved

Sponsors must also attest that the trial will be conducted according to good clinical practices (GCP).

Depending on the decentralized activities within the proposed trial, sponsors should describe in their CTA:

- how clinical trial activities and participant visits are expected to be conducted (for example, in person, by telephone or telehealth platform)
- how the proposed decentralized approach is in keeping with the risk posed by the trial to participants

Conducting a clinical trial with decentralized elements

As per Division 5 of the regulations, including sections C.05.010 to C.05.015, sponsors and investigators must adhere to GCP to ensure that investigational drugs are used properly in a clinical trial. This includes meeting requirements on:

- submission of information
- drug labelling to meet the requirements of section C.05.011 of Part C, Division 5
- ensuring that a clinical trial drug is manufactured, stored and handled according to good manufacturing practices (GMP)
- record keeping for the required record retention period to enable accurate reporting, interpretation and verification
- reporting suspected unexpected serious adverse reactions (SUSARs)
- informed consent
- validated digital health technologies

Sections C.05.010 to C.05.015

Health Canada inspects clinical trials to assess adherence to GCP, according to the following guidance:

- Good clinical practices for drugs for clinical trials involving human subjects (GUI-0100)

Find more information in the section on inspections.

Sponsor's obligations

Sponsors should consult other relevant policy and guidance documents, such as:

- Guidance document for clinical trial sponsors: Clinical trial applications
- Tri-council policy statement: Ethical conduct for research involving humans
- Tri-agency research data management policy

In general, sponsors are responsible for coordination, logistics, maintaining records of personnel and activities, and reporting SUSARs, among other activities. Sponsors must also ensure that the clinical trial and the drug comply with the approved protocol and applicable laws and regulatory requirements. This includes provincial or territorial statutes on informed consent, privacy and health records management.

Sponsors must implement a quality system consisting of documented procedures (for example, standard operating procedures or SOPs, protocol procedures) to ensure quality of every stage of the trial process and at all sites. Such a system should comply with the regulations and ICH E6.

Decentralization of clinical trial activities across third parties and locations could complicate oversight and monitoring of trial activities. Sponsors should develop and implement robust, comprehensive plans (or written procedures) for the decentralized elements to help them:

- monitor and oversee trial conduct at all locations to ensure compliance with the protocol and applicable legal and regulatory requirements
- manage data and records generated by the trial to support compliance with regulatory requirements related to records handling, data capture and validation, data entry and monitoring, and data storage
- identify, document and report adverse events in a timely manner as specified by the regulations, given potential delays in communication between the locations where trial activities occur and the clinical trial site
    - Find information on safety reporting, including reporting criteria and process, in Section 5.14 of Guidance document on drugs for clinical trials involving human participants (GUI-0100).
- disseminate critical information, for example, for the timely review of test results and patient monitoring
- support validation and calibration of technical instruments and measuring devices across decentralized locations
- ensure the integrity of the investigational product is maintained when transported and stored to safeguard participant safety throughout the trial and address any potential risk of diversion of any controlled substance used in a trial
- monitor participant compliance with the therapy
- effectively coordinate third parties or contracted services

Where a trial involves several physical locations, sponsors should ensure the informed consent process is carried out in a way that mitigates risks to participants and maintains appropriate records of participant consent.

When identifying trial-related personnel or other third parties involved in trial activities, sponsors should take appropriate measures to ensure that:

- everyone involved in trial activities is qualified by education, training and experience, and meets the necessary standards for the conduct of the clinical trial activity
- they maintain or have access to records of qualifications through education, training and experience of everyone involved in trial activities, where applicable
    - In some cases, such as routine procedures (blood tests, medical imaging) or non-study-related care provided ad hoc (such as emergency room visits), Health Canada recognizes that this documentation may not be readily available.
- identified third parties can undertake the delegated activities, for example, ensuring that local health care providers or contracted service providers:
    - are qualified and trained to conduct delegated activities
    - have the resources they need to maintain participant safety

Investigator responsibilities

QIs may delegate specific trial-related activities to qualified trial personnel or other third parties, including local health care providers and contracted service providers. QIs are responsible for:

- ensuring that the trial at their site (and at any associated decentralized locations) is being conducted with the appropriate oversight and that participant safety is protected
- supervising medical care and medical decisions related to the clinical trial at all locations associated with their trial site

When delegating trial-related activities to trial personnel or other third parties, QIs must ensure that:

- all delegated activities are conducted according to the approved protocol, applicable regulatory requirements and GCP
- identified third parties have the capacity, knowledge and experience to undertake the delegated activities

Training and qualification

A range of trial-related activities may be delegated, and could include:

- procedures requiring specific knowledge of the trial protocol, investigational drug, investigator's brochure or the investigational drug under study
- procedures requiring some knowledge related to participant safety (identifying possible adverse events), but that fall within the standard scope of practice of local health care providers
- routine procedures (for example, blood tests or medical imaging) or non-study-related care provided ad hoc (such as emergency room visits)

Sponsors and QIs should document the specific training required for the activity to be conducted by delegated personnel. Training requirements should be flexible to minimize unnecessary burden for participating health care providers while ensuring that delegated activities are conducted safely and according to the protocol.

In general, training should be relevant to the study-related duties and include the relevant sections of trial protocol for which the person is responsible to carry out. If applicable, training should also be provided on relevant supporting guidance, including, for example, ICH E6.

For example:

- Some activities may require detailed knowledge of the protocol and investigational drug under study. They should be conducted by personnel who are appropriately trained on the protocol and relevant supporting guidance, such as ICH E6 and Part C, Division 5 regulatory requirements for delegated trial-related duties.
- Other delegated activities such as follow-up visits with local health care providers may only require knowledge of the investigator's brochure and how to report SUSARs according to regulatory and ICH E6 requirements. Training on supporting guidance, such as ICH E6, may not be required in all cases.
- Procedures that are routine (such as a routine blood test or medical imaging) or are part of non-study-related care provided ad hoc (such as emergency room procedures) do not require specific training and delegation from the QI.

Oversight and delegation log

QIs must oversee delegated activities throughout the trial. Accordingly, they should implement procedures to:

- supervise and monitor the conduct of the trial-related activities, including those operating in decentralized or remote settings
    - This may include, for example, regular established supervision meetings.
- ensure the security and integrity of the data generated by the trial, at a main site and all other related locations
- ensure appropriate record-keeping for trial-related records (either paper or electronic) such as the delegation log and agreements
    - Trial-related records must be available at the main location (associated with the QI) of the clinical trial site.

QIs must maintain a delegation log, available at the main location of the clinical trial site (associated with the QI). The delegation log must clearly identify all persons to whom study-specific responsibilities have been delegated.

The delegation log should also:

- be developed before the trial begins and updated as necessary
- be signed and dated by the QI before a task is delegated
- contain tailored training requirements for persons or occupations involved in specific trial-related activities
    - Not everyone in the delegation log is required to have the **exact same** research-training requirements.

Trial-related documentation (for example, supervision plans) should distinguish between activities requiring delegation and training, and those that fall within routine clinical practice.

QIs do not need to include the following procedures in the delegation log. However, they should take appropriate measures to ensure that the individuals involved are qualified and that their planned involvement is clearly outlined in trial-related documentation:

- routine procedures (for example, a routine blood test or medical imaging) **or**
- non-study-related care provided ad hoc (such as emergency room procedures)

For these types of procedures, Health Canada recognizes that, within reason, documentation on the qualifications of all third-parties may not be readily available to the QI.

For more information on delegation logs and training for clinical research, consult:

- Guidance document on drugs for clinical trials involving human participants (GUI-0100)

The delegation log and other relevant documentation to manage delegated activities must be available at the main location of a clinical trial site and may be requested by Health Canada during an inspection. Note that this documentation includes any established contracts or agreements between the sponsor and other third parties, institutions or locations outlining specific roles, responsibilities, liabilities and indemnities.

Informed consent process

Sponsors must inform participants of the risks and anticipated benefits of participating in the trial. Informed consent must comply with the applicable laws and regulations governing consent:

- ICH E6 requirements
- provincial and territorial rules and regulations
- REB approval of the informed consent process, including the Informed Consent Form (ICF)

For decentralized clinical trials, the informed consent process may involve the QI (or delegated persons) at a main location and participants at other physical locations.

If applicable, trial-related documentation should support:

- any delegating of duties related to the informed consent process to trial personnel or other third party
- obtaining informed consent through a virtual meeting (for example, at a health care provider's office or potential participant's home)
- the proposed medium of the documented record of participants providing their consent (for example, written, video, audio)

Sponsors and QIs should establish a process for how informed consent will be obtained according to ICH E6 requirements. The process should give potential participants information on the following:

- the trial and decentralized trial activities that are relevant to their decision to participate
- who to contact if they have questions about the research
- a 24-hour number or who to contact if they have a research-related injury (for example, local health care provider, emergency services, QI)
- who will have access to their personal health information collected during the trial and how it will be securely stored and transferred
- the retention of a documented, retrievable and attributable record of the participant's informed consent

Virtual meeting platforms and electronic signatures may make the informed consent process more efficient for those who live in remote areas. However, sponsors should be

careful not to create a disadvantage for those who do not have access to or prefer not to use virtual platforms. Doing so may introduce ethical considerations related to fairness and equity.

Consider:

- providing different methods of informed consent to those who request them, including in-person consent meetings and physical copies of the ICF
- a virtual meeting platform that includes both audio and video so that QIs (or delegated persons) and participants can participate in the informed consent process in real time, and interact with a real person if it is their preference

Virtual platforms and digital technologies bring concerns about privacy, confidentiality and trust, as well as the need to verify the accuracy of information provided by generative models (artificial intelligence). Such technologies must be validated for their intended use and could require additional security measures to protect participants' personal information and safety.

During an inspection, Health Canada will verify that:

- an REB reviewed and approved the informed consent process
- procedures are correctly documented
- participants have access to their informed consent records
- informed consent records are available for inspection

Clinical trial inspections

Health Canada monitors clinical trials through inspections to ensure that clinical trials are being conducted according to legal and regulatory requirements. During an inspection, inspectors assess that clinical trial activities comply with regulatory requirements, applicable standards and the approved protocol.

In decentralized clinical trials, the main location of the clinical trial site (associated with the QI) is the main point of contact for an inspection. Health Canada inspectors may ask sponsors and QIs to provide documents demonstrating adequate coordination, oversight and monitoring of delegated parties and the protection of participant safety.

Health Canada may inspect other physical locations where study-specific activities take place. We identify these locations based on the risk associated with the types of delegated activities being conducted there. Proper documentation at the main location can help inform whether there is a need to inspect any other decentralized location associated with that site.

In general, routine or ad hoc procedures that don't involve protocol-specific elements and are performed in settings such as a medical imaging clinic or hospital emergency department are not subject to inspection.

Sponsors should consider the inspection process from the outset when designing a decentralized clinical trial, especially around planning trial activities in participants' homes. For example, Health Canada may need to enter a home if the clinical trial activity occurring there poses a hazard to a participant. Recognizing that an inspection in a home may invade a participant's privacy, sponsors should ensure that trial-specific procedures are conducted in appropriate settings according to the risk or hazard posed to participants. If it's expected that study-related procedures will take place in a participant's home, the participant must be told that an inspection may take place as part of the informed consent process.

For virtually conducted activities involving other locations, all related information and records must be accessible for inspection from the main trial location.

For an investigational drug that requires specific storage conditions, Health Canada inspectors may request documentation so they can assess if the drug was stored appropriately when being transported to remote locations. This may mean ensuring that shipping containers and configurations offer the required conditions (for example, 2°C to 8°C, keep frozen, prevent from freezing) for the maximum expected transport time.