

**Initiative to Streamline Clinical Trials (ISCT):
Guidance for Investigators/Sponsors**

ISCT Recommendations

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1. Summary and Key Recommendations

a) Background and ISCT

The 2011 Canadian Cancer Research Alliance (CCRA) report on the State of Cancer Clinical Trials In Canada outlines in detail the magnitude of the threat to the conduct of oncology clinical trials. The Report noted that with falling performance metrics, increasing complexity and workload, and an increasingly onerous regulatory environment, clinical trials were at risk, and observed that “Without clinical trials, the outcomes of cancer patients will not continue to improve”. The report recommended engaging with Health Canada and other key stakeholders to foster agreement in appropriate interpretations of the Health Canada Food and Drug Regulations and ICH Good Clinical Practice (GCP) guidelines.

In 2013, The Organisation for Economic Cooperation and Development (OECD) published a report entitled “OECD Recommendation on the Governance of Clinical Trials”

<http://www.oecd.org/sti/sci-tech/oecd-recommendation-governance-of-clinical-trials.pdf>

recommending that Members adapt their national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials. This is in keeping with other risk-based recommendations including the FDA's “Guidance for Industry Oversight of Clinical Investigations, A Risk-Based Approach to Monitoring”, August 2013.

In 2012, the Senate Report: Canada's Clinical Trial Infrastructure was released and addressed issues such as infrastructure, clinical trial registration, orphan drugs, risk-based approaches for monitoring and Adverse Event (AE) reporting, public access to clinical trials information and changes to the Food and Drugs Act to allow the recommendations/modernization

The Initiative to Streamline Clinical Trials (ISCT) Working Group, formed in 2012 to address the CCRA recommendations, includes members who are experts in clinical trial conduct across many therapeutic areas. The primary objective of the ISCT was to develop specific, pragmatic and practical interpretations of current regulations, laws and guidelines, in order to facilitate, rather than limit, Canadian clinical trials, by expanding on recommendations such as those of the CCRA and OECD. During the discussions, it became apparent that changes to certain regulations or laws interpretations were also desirable.

The focus of ISCT encompassed *academic* clinical trials of *drugs and/or biologics* which are required to be, or interpreted as required to be *conducted under a Clinical Trials Application*. Academic trials are defined as trials where the regulatory sponsor of the clinical trial is *not* a commercial for-profit organization such as a pharmaceutical company or contract research organization (CRO).

Academic trials are an important and independent tool in developing and understanding the true clinical benefit of new therapies in all disease areas and provide critical validation (or in some instances, has called into question the results) of research conducted by a for-profit entity. Academic / cooperative groups play a unique role in addressing research questions of societal interest and produces important answers that inform our health care policies and the next generation of research questions. Urgent action is needed to ensure that academic clinical trials continue to be conducted given the threat to the viability of such trials.

b) Issues and Concerns

Feedback was obtained from interested parties, as well as ISCT members, by means of surveys, face-to-face meetings and conference calls. The major areas of concern identified included Clinical Trial Applications, drug supply, monitoring, oversight of equipment and facilities, delegation of duties, validation of electronic systems, source documents and records retention, trial costs and other areas such as consistency of interpretation by different divisions of Health Canada and access to, and utility of, website resources and information.

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c) Identified Areas of Concern

For each area of concern identified above, a subcommittee was formed and a series of recommendations and suggestions were made that would allow the streamlining and continued success of academic clinical trials.

- All members were in agreement that the OECD framework and recommendations should be adopted and implemented in Canada.
- Although the principles in the OECD recommendations are helpful, there are areas where explicit interpretation and further recommendations, which might include amendments to current regulations, were felt critical for the continued viability of academic clinical trials. These include:
 - Drugs and regimens long used as standard-of-care in Canada but which do not always have a specific indication in the product monograph
 - Drugs used in a clinical trial which are supportive or not part of the research question.
 - The role of central monitoring of participating sites and the careful definition of critical data elements and acceptable source documents.
 - Standard-of-care equipment that is not critical to the research question considered to be under the oversight of the clinical trial staff/unit
 - Retention of records not consistent with institutional policies
 - What data points require formal review by the Investigators
 - Participants logs and delegation of duties specific to the clinical trial, rather than standard-of-care (e.g. requiring volunteers who weigh patients to be trained and on the log)
 - Alignment of CIHR guidelines (which do not allow expenses for regulatory compliance) and Health Canada regulations
 - Consistent interpretation and observations by Health Canada across all sites

ISCT Recommendations

d) Summary of Specific Recommendations

	Feasible	Recommended
CTA and Safety Reporting		
OECD framework and recommendations should be adopted and implemented in Canada within the existing regulatory framework	✓	
Appropriately justified standard –of-care drugs do not require a CTA	✓	
Consistent interpretation of risk and maintenance of a database of decisions	✓	
Consider a joint academia-regulatory initiative is recommended where consensus interpretations can be made	✓	
Only risk-based, relevant and justified processes for safety reporting and concomitant medication collection should be planned	✓	
For lower risk trials, limit expedited SAE collection to related and unexpected events, and consider collecting only AEs, and grade/severity of events, of interest	✓	
If needed, amend regulations to allow standard-of-care drugs to be considered low risk and OECD Category A		✓
Drug Accountability and Labelling		
Drugs used in a clinical trial, for which a CTA has not been filed (Category A trials), should be managed as commercial drugs and standard pharmacy/dispensing practices/policies followed.	✓	
Category B drugs which are commercially available, for which a CTA has been filed, should be managed as commercial drugs and standard pharmacy practice followed; trial-specific drug accountability logs are required <i>only</i> for drugs specifically labeled as clinical trial supply.	✓	
On-site monitoring of drug/pharmacy is rarely required for category A and B trials where commercial stock is used.	✓	
Monitoring		
ISCT is in agreement with recommendations of the FDA and the OECD with respect to implementation of a risk-based approach to monitoring	✓	
Central monitoring of <i>selected critical</i> study parameters and data elements should be the primary strategy for academic trials	✓	
Limited on-site monitoring may be appropriate for higher-risk Category B trials and for some Category C trials. The monitoring plan should allow for risk based adaptation of monitoring depending on deviations or data trends identified throughout the course of the trial	✓	
Risk based and justified monitoring plans should be summarized in the protocol or an appendix allowing review and approval by Health Canada during the CTA review process	✓	
Equipment and Facilities		
“Research equipment” for clinical trials should be defined as equipment used solely for the purpose of a clinical trial and unrelated to the delivery of standard-of-care. The responsibility for maintenance and calibration of such equipment rests with the Institution	✓	
An assessment of risk and acceptability of institutional programs should be conducted prior to implementing a trial specific equipment maintenance process.		
Requirements for maintenance of equipment designated as research should be	✓	

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	Feasible	Recommended
documented appropriately and prospectively in the protocol or an appendix. Inspectors should use that agreed plan when conducting site inspections		
Delegation of Trial Related Duties		
Roles required as part of standard-of-care, or as part of care provided on an <i>ad hoc</i> basis, are not required to be documented as part of the trial delegation log (e.g. imaging, emergency room staff).	✓	
If a specific trial-related task requires a level of training beyond the usual scope of practice, or requires a specific professional to conduct the task, it will be stated in the protocol or in the operational documentation from the study sponsor. Otherwise, tasks can be delegated by the QI to an individual qualified to perform that task or process, and no additional training (other than study specific training) is required.	✓	
The delegation list, either the initial list or any modified version, should be created and maintained by the QI, or delegate, in a timely manner. Verbal authorization from the QI to begin a trial-related task is permissible, with the delegation log to be revised within an acceptable window, to be determined and prespecified by the sponsor. Sign-off of each change to the delegation list by the QI is not required if the task is delegated appropriately.	✓	
CVs and other documentation (e.g. financial disclosures) are only required for the QI and sub-investigators, provided that other staff, who are delegated tasks, are employees of the institution.	✓	
Validation of Electronic Systems		
An electronic system used as the permanent record for regulatory purposes needs to be validated for its intended use and records retained in accordance with the Regulations. Processes of the software development and deployment need to align with Software Development and System Operation Good Practices, and be appropriately documented	✓	
The level of validation of the electronic system needs to be consistent with complexity, level of customization, and overall risk assessed.	✓	
Requirements and Policies related to the retention of records need to align with Institutional Policies where applicable.	✓	
Source Documents and Record Retention		
For documentation identified as requiring a review in the protocol, there should be a record that either the QI or sub-investigator has reviewed the protocol- defined out-of-range results.	✓	
The protocol should identify those data elements requiring source documentation, and sites can then declare the type of source documents (e.g. chart-based, e-record, a combination).	✓	
Investigators are not required to store electronic CRFs (eCRFs) after study completion if data have been collected through an electronic database. The sponsor will store these data.	✓	
Record retention policies will be according to institutional policies. If the trial data are being used to support a marketing application, once all data are collected and quality assurance policies completed, on-site data storage need only follow institutional policies. The sponsor will keep these data for 10 years after marketing		✓

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	Feasible	Recommended
application submission. This will require a change to the Food and Drug Act		
Trial Costs		
CIHR funding guidelines and eligible expenses for clinical trials conducted under a Health Canada CTA must be aligned with Health Canada regulations to allow for the payment of essential expenses related to regulatory compliance. This would include regulatory support for CTA submissions, study monitoring and oversight activities, research ethics board fees, and clinical trial insurance	✓	
Other		
For academic trials a simple, short standard questionnaire for the site to complete prior to an inspection would provide some context to the inspector on how the site operates (i.e. do other facilities participate in the research process).	✓	
Health Canada might consider a default period for approval of corrective action plans, where approval is understood after a default of 30 days		
ISCT recommends that training can be demonstrated by the following: certificates, CVs, minutes of meetings (with attendance), signed note to files, but that template documents should be provided that includes required sections (date, duration, trainer, agenda, and attendees). People need to be trained only on relevant areas and people performing standard-of-care processes (e.g. standard laboratory tests or administering standard –of-care chemotherapy) do not need trial specific training or to be on the delegation list unless the processes are trial specific.	✓	
The Health Canada website could be improved by the inclusion of a site map - specifically for Clinical Trials. The addition of an advanced search function would also allow for more appropriate hits.	✓	
ISCT recognizes the complexity of organizational structures and processes within the Federal government and Health Canada, and the difficulty with ensuring consistency and efficiency across multiple organizational parts, especially with different reporting structures, which may be regional. Nonetheless, the impact of this on the academic research community is very costly (in terms of both dollars and resources). Clear, simple and consistent processes and interpretation, would significantly improve the access of Canadians to non-commercially driven trials, which have been proven to improve outcomes. This recommendation, in the opinion of ISCT, is critical.		✓

e) Next Steps

The final Recommendations of the ISCT will be provided to all Stakeholders and published on an ISCT specific website/page. All Stakeholders will be asked to provide links to the Recommendations on their websites and ensure their members are aware of the ISCT Recommendations. The website will also provide access to sample documents and forms that may be useful to Stakeholders, and will also provide a portal for notification of planned/new academic clinical trials and which area/s of the Recommendations have been implemented so that the impact can be assessed periodically. The Recommendations will be summarized in a manuscript and submitted for publication in a relevant Journal. The ISCT will further evaluate the impact of the Recommendations on the conduct of academic clinical trials in Canada by means of annual surveys of Stakeholders, review of changes to regulations and laws, review of Inspectorate findings as well as ongoing dialogue with Health Canada. The ISCT will collaborate with CCRA, CPAC and CCCTN in plans for updating the 2011 report “The State of Cancer Clinical Trials In Canada”.

2. Introduction

While all acknowledge that clinical trials are critical to the development of new therapeutics and treatments that will ultimately result in societal benefits, changes in the regulatory oversight of academic clinical trials in the past decade have resulted in increased complexity and cost (1, 2), and are perceived to have discouraged the continued development of academic clinical trials in Canada. New initiatives to tailor the interpretation of regulations and guidelines, or to change regulations to reflect the real risk to subject safety and/or scientific rigor, have been proposed and are being implemented internationally. ISCT seeks to build upon those initiatives for the Canadian context.

a) The Canadian Cancer Research Alliance Report

The Canadian Cancer Research Alliance (CCRA) report on the State of Cancer Clinical Trials In Canada, Oct 2011 <http://www.ccra-acrc.ca/PDF%20Files/CT%20report%20Oct%202011.pdf> outlined in detail the magnitude of the threat to the conduct of oncology clinical trials. “Without clinical trials, the outcomes of cancer patients will not continue to improve.” The major findings documented in the report include:

- Cancer clinical trials performance metrics are falling
- Institutional clinical trials units are under stress
- Trial complexity has increased
- Regulatory environment has changed and is more onerous
- Workload of research ethics board (REB) is increasing

The key recommendations include:

- Create a pan-Canadian infrastructure program that supports cancer clinical trials
- Streamline the clinical regulatory environment
- Consolidate or develop reciprocity in Research Ethics Boards
- Reduce non-value-added steps in trial development and conduct.

The report recommended engaging with Health Canada and other key stakeholders to foster agreement in appropriate interpretations of the Health Canada Food and Drug Regulations and ICH Good Clinical Practice Guidelines, to improve the efficiency of clinical trials, reduce the resource and costs associated with these requirements while ensuring or enhancing patient safety.

b) The Organisation for Economic Cooperation and Development (OECD) Report

OECD Recommendation on the Governance of Clinical Trials (2013) recommends that members adapt their national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials.

<http://www.oecd.org/sti/sci-tech/oecd-recommendation-governance-of-clinical-trials.pdf>

This approach classifies trials into 3 categories that reflect the risks involved:

Category A (authorized medicinal products, according to national or regional regulations, tested in accordance with their marketing authorization). Regulatory approval is not required, commercial product can be used without trial specific labels, and should labeling be necessary, standard pharmacy procedures can be used (not Good Manufacturing Principles (GMP)), product monographs (rather than investigator brochures) are acceptable and quality management plans focus on mitigating key risks.

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Category B (authorized medicinal products tested according to treatment regimens outside their marketing authorization, in terms of population, condition, administration, or dosage). This category may be either *supported* by published evidence or guidance or established medical practice (B1) or *not supported* by published evidence or guidance or established medical practice (B2). Both require formal regulatory approval, and for B2, require insurance to be in place (for academic trials, general institutional liability, medico-legal), but otherwise may be managed according to the principles recommended for category A.

Category C (clinical trials on medicinal products without any marketing authorization). Require regulatory approval and full compliance with GCP and GMP requirements, including the provision of an Investigator Brochure.

c) Senate Report: Canada's Clinical Trial Infrastructure

In November 2012, the Senate report was released and identified a number of recommendations pertaining to clinical trials:

<http://www.parl.gc.ca/Content/SEN/Committee/411/soci/rep/rep14nov12-e.pdf>

- (1) Leadership role in clinical trials infrastructure, including developing a National Framework for Coordinating Clinical Trials (NFCCT)
- (2) Require clinical trial registration for all phase 2 and 3 trials
- (3) REB accreditation program
- (4) Mandate the use of accredited REBs
- (5) NFCCT encourage research networks, centralize ethics review and database creation of potential participants
- (6) Require testing in relevant populations
- (7) Create orphan drugs status and ease requirements
- (8) NFCCT promote and facilitate trials for orphan drugs
- (9) Create expert committee to consider intellectual property and tax incentive options to facilitate Canadian competitiveness in drug development
- (10) Strengthen risk-based approaches for monitoring and Adverse Event (AE) reporting, notification of non-compliance and public access to clinical trials information as well as increase inspections and require electronic reporting of Adverse Drug Reactions (ADR)
- (11) Pursue necessary changes to the Food and Drugs Act to allow the recommendations/modernization
- (12) Health Canada to monitor and evaluate the impact of the recommendations on clinical trials in Canada.

d) The Initiative to Streamline Clinical Trials (ISCT)

The Initiative to Streamline Clinical Trials (ISCT) Working Group was formed in 2012 to address the CCRA recommendations. The Working Group (Section 14, Table 1) includes experts in clinical trial conduct across several therapeutic areas; members have clinical trial roles ranging from academic investigators to Cooperative Group members.

The primary objective of the ISCT was to develop specific, pragmatic and practical interpretations of current regulations, laws and guidelines in order to facilitate, rather than limit, Canadian clinical trials, expanding on recommendations such as the CCRA, OECD and Senate recommendations.

The ISCT developed terms of reference, assigned a Chair and Co-Chairs, and planned to define scenarios where guidance might safely reduce cost and complexity with regards to:

- Whether a Clinical Trial Application (CTA) and regulatory approval was required
- Level/extent of monitoring needed
- The data that must be collected and reviewed
- Inspection findings

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- Obtaining data to support the recommendations based on retrospective review, and considering the development of prospective measures and metrics
- Gaining consensus across Canada and all therapeutic areas
- Writing a position paper/draft guidance document for review
- Organizing a larger meeting with all stakeholders to review and approve the guidance, and plan implementation.

Although Health Canada is responsible for the oversight of clinical trials of natural health products, pharmaceuticals, biologic agents and medical devices, the predominant focus of ISCT encompassed **academic clinical trials of drugs or biologics**.

e) Academic Clinical Trials

The focus of the current initiative concerns only academic trials which are required, or could be interpreted as being required, to be conducted under a CTA.

Academic trials are defined as trials where the *regulatory sponsor* (i.e. the individual, group or institution who would file the CTA, if required) of the clinical trial is not a commercial for-profit organization such as a pharmaceutical company nor a contract research organization (CRO). Academic research is generally different in scope than for-profit research, and is less likely to include comparative bioavailability or equivalency studies, and is more likely to include phase 2 and 3 trials involving marketed products where the proposed use is outside the Notice of Compliance (NOC) or Drug Identification Number (DIN) application. Other scenarios include trials which ask questions which are of little interest to commercial for-profit organization, but important for society and patient management, such as trials testing new drugs in children or rare diseases, the use of off-patent drugs, or increasingly N-of-1 trials based on genomic testing.

Academic trials are an important and independent tool in developing and understanding the true clinical benefit of new therapies in all disease areas and provide critical validation (or in some instances has called into question the results) of research conducted by a for-profit entity. Urgent action is needed to ensure that academic clinical trials continue to be conducted given the threat to the viability of such trials.

f) The Process

The ISCT Steering Committee designed a web-based survey and solicited input from interested parties across Canada (Section 14, Table 2). Respondents were asked to identify and rank aspects of the conduct of clinical trials that have resulted in increased budget or resource requirements and have impacted on their ability to conduct academic clinical trials, either as a participating site, or as an academic sponsor.

Areas of concern identified included:

- Clinical Trial Applications
- Drug or Product Supply
- Monitoring Requirements
- Oversight of Equipment and Facilities
- Delegation of Trial Related Duties
- Validation of Electronic Systems
- Source Documents and Records Retention
- Trial Costs
- Training and Contracts

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For each area, leaders were identified and asked to form small subcommittees which met by conference call. Laws or regulations were identified and current interpretation was summarized using sources such as the Health Canada Inspection findings, as well as data collected by ISCT members. After careful review, suggested interpretations and recommendations were developed and reviewed by the ISCT. Each recommendation was identified as being either **feasible** (i.e. could be implemented without changes to the Canadian regulations) or **recommended** (i.e. where changes to regulations would likely be required, and were for further discussion and consideration). A draft document was prepared and reviewed with stakeholders, and then discussed with various divisions of Health Canada, including the Health Protection Branch (HPB) and the Inspectorate. The document was revised and circulated for final approval and implementation.

Although the ISCT originally planned to focus on recommendations for interpretations of existing regulations and laws, it became clear during the process that two additional barriers existed for the successful streamlining of academic clinical trials. Firstly, some areas of regulations were felt to be so explicitly defined that there was little flexibility in interpretation, and meaningful change would require revisions to the Food and Drug Regulations. Also, in a more operational sense, consistency in interpretation was hard to achieve due to the diverse organizational structure of Health Canada itself, with oversight by different Deputy Ministers. While some suggested recommendations, such as the explicit definition of what constituted research equipment in the protocol, might be approved by the HPB through the CTA review (suggesting Health Canada agreement), the Inspectorate, a separate organization reporting to a different Assistant Deputy Minister and regionally structured, responsible for ensuring compliance with regulations, might not consider that compliant during site inspections. Further, it became apparent that there are regional differences in the interpretation of regulations by Inspectors.

The recommendations, therefore, and as noted above, identify areas where the ISCT consider it 'feasible' to implement by re-interpretation of the regulations, and 'recommended' where ISCT believe changes to regulations or laws may be required.

g) Applicable Regulations

According to Health Canada Regulations, an [investigational] "drug" means a drug for human use that is to be tested in a clinical trial. The ISCT Recommendations, therefore, only apply to drugs that are the subject of the testing in the clinical trial. Any other drugs included in a protocol for which there is no intention to discover or test the effects of that drug, and no analyses are planned or done regarding the drug and its effects, are not investigational drugs under the above definitions.

The following regulations and documents are referenced for this document:

- The Health Canada Food and Drug Regulations C.05.010 Good Clinical Practice (GCP), and GCP 5.18.3
- Health Canada Guidelines for Temperature Control of Drug Products during Storage and Transportation <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069-eng.php>
- Health Canada Good Manufacturing Practices http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/compli-conform/gmp-bpf/docs/gui-0001-eng.pdf.
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002
- E11: Clinical Investigation of Medicinal Products in the Pediatric Population and Health Canada Addendum to the ICH 1 Guidance E11: Clinical Investigation of Medicinal Products in the Pediatric Population
- Annex 11 Good Manufacturing Practices (GMP) Guide: Computerized Systems
- ICH GCP 5.5.3

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- Health Canada Guidance for Records Related to Clinical Trials (GUIDE-0068)
- FDA's Guidance for Industry for Computerized systems used in Clinical Trials: Computerized Systems Used in Clinical Trials, September 2004
- FDA's Guidance for Industry Oversight of Clinical Investigations, A Risk-Based Approach to Monitoring, draft guidance, August 2011.

For research conducted in collaboration with USA academic groups:

- Office of Human Research Protections (OHRP),
- Code of Federal Regulations (Title 45 CFR Part 46),
- NCI US Clinical Trials Monitoring Branch Guidelines for Auditing of Clinical Trials

3. Clinical Trial Application

a) Background and examples of identified issues

Expectations for when a CTA should be filed have greatly expanded under the current Division 5 regulations, and are not currently risk-based. The requirement to file a CTA to Health Canada has significant resource and cost implications. Incremental costs include those related to filing the CTA, regulatory documentation reporting and monitoring. While some of the academic groups have developed processes for conducting and overseeing studies under a CTA, including pharmacovigilance and on site monitoring, for an individual investigator, the barriers of cost, time and expertise have been steadily increasing and are daunting.

Although the OECD recommendations provide a useful framework to identify trials for which a CTA must be filed, there are a number of areas which remain open to interpretation with respect to the Health Canada Division 5 regulations.

- ❖ A frequent area of discussion relates to protocols that include more than one drug or intervention. This may impact whether a CTA is required at all, and even if required, for which drugs the CTA is filed.
 - A drug used in an approved indication, given with another standard therapy (either another drug or radiation therapy or surgery). Is this a Category A trial, or is this a 'new' combination and therefore an [OECD] Category C trial? ISCT considers that when there is no plausible reason to expect significant clinical effects on pharmacokinetics (for example, the use of a monoclonal antibody with an oral agent) nor incremental toxicity, and where a substantial safety database exists for the drug, a designation as Category A may be reasonable.
 - The use of supportive care drugs (e.g. growth factors, prophylactic antibiotics, chemo-protectants) with a chemotherapy regimen. If the chemotherapy regimen is not used in an approved indication (i.e. a category B or C trial), must the supportive care drugs be considered in the same category and, therefore, be subject to the same requirements with regard to drug supply, labeling and equipment maintenance? ISCT considers that supportive care drugs used in indication or as standard-of-care (see below for definitions) should not be considered as investigational and that Category A considerations apply;
- ❖ If a drug is being used in an approved indication with a minor variance in schedule or patient population with no anticipated safety implications, can this be considered Category A in select circumstances?
- ❖ The incidental inclusion of a standard-of-care drug-based treatment in a surgical trial.
 - An example is the NCIC CTG SHAPE CX.5 trial which compares radical vs. simple hysterectomy in cervical cancer. While the question is purely a surgical one, the standard-of-care is to offer post-operative chemo-radiation to high-risk patients as detailed in Provincial Formularies (3). The sponsor was required to file a CTA, resulting in major issues with the participation of academic groups outside of Canada, and thereby threatening its viability. If chemo-radiation in this setting is considered standard-of-care, can this be considered Category A? Requiring CTA filing for academic trials, such as this one in which the research question is purely a surgical one, appears to add cost and complexity without adding value or increasing safety.
- ❖ Drugs used in the pediatric setting, as well as in adults in some circumstances, where there are no data or specific indications included in the Product Monographs of many marketed drugs, were identified as a specific concern. Many drugs approved in Canada were approved with no pediatric specific labeling, or with a single original indication, yet there often exists a broad base of research and they have been widely

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used as standard clinical care for many years. Are such trials/drugs classified as Category B1, or could they be considered in select and justified circumstances, for academic trials, as Category A. Even of even if a CTA must be filed for investigational drugs being used in the trial costs and complexity will be reduced.

- ❖ Rare diseases that have small patient populations are also lacking in clinical trials research data from pharmaceutical companies. Reviewing and accepting research from sources other than pharmaceutical company data may be necessary to accurately assess risk benefit, for drugs with well-established pharmacokinetic and toxicity profiles.
- ❖ There may be some instances where what appears to be a Category C trial may in fact be considered low risk. Examples include where a drug/product has regulatory approval in other jurisdictions, based on extensive clinical studies but for commercial or patent reasons is not marketed in Canada.

b) When, and for which drugs, should a CTA be submitted?

The ISCT supports the OECD recommendations and their implementation in Canada. Drugs defined as supportive care for the patient population or condition under study should be recorded as needed, but do not meet the definition of a drug being tested in a clinical trial.

Drugs used as a standard-of-care comparator arm are, by definition, no longer investigational and are not Investigational Products (IP). Standard-of-care can be defined as treatment used based on one or more of the following: marketing authorizations, provincial formulary designation as standard and or funded therapy, systematic reviews, recognized clinical practice guidelines or robust phase 3 clinical trial publications.

Academic sponsors should provide clear justification and reference supporting information such as Formularies and Practice Guidelines:

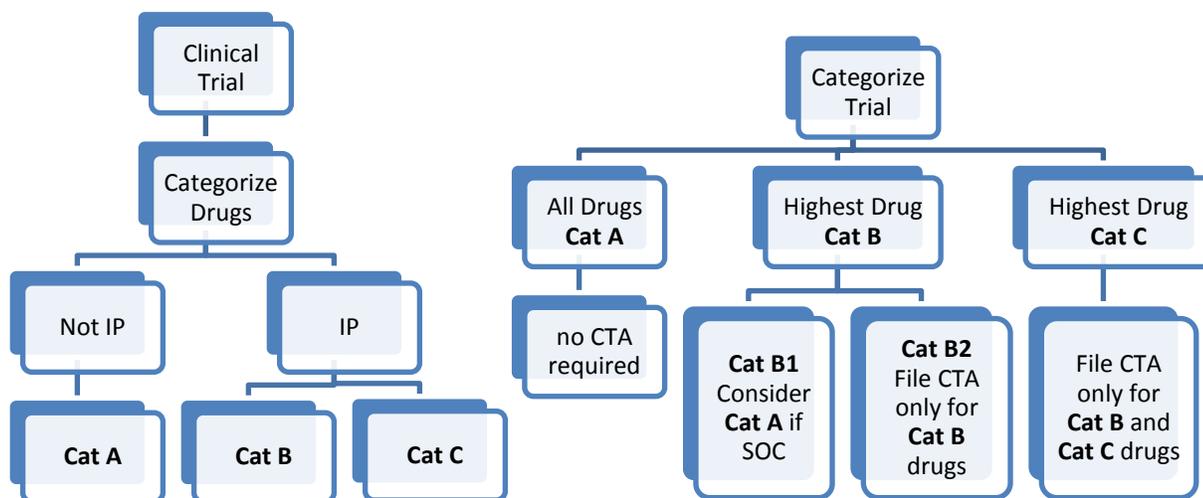
<http://www.bccancer.bc.ca/HPI/ChemotherapyProtocols/default.htm>

<https://www.cancercare.on.ca/toolbox/drugs/drugformulary/>

<https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10144>

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Suggested CTA Submission Approach Based on OECD Risk Categories



SOC, Standard-of-Care; Cat, Category; CTA, Clinical Trial Application; IP, Investigational Product.

Scenario	Interpretation
Category B or C Investigational Product	Submit CTA
Category B or C Investigational Product with standard treatment or supportive drugs ^{1,2}	Submit CTA only for category B or C Investigational Product
Category B or C Investigational Product with drug/treatment which cannot be justified as standard treatment ³	Submit CTA for category B or C Investigational Product and non-standard treatment
Pediatric clinical trials where no specific regulatory approval exists but 'standard-of-care' drugs are used (either alone, or as part of the trial)	Careful consideration of the appropriate categorization is required in consultation with Health Canada. In many instances standard treatments may be considered Category A
¹ Used in dose and schedule approved by Health Canada or described in Provincial Formularies, systematic reviews, recognized clinical practice guidelines or robust phase 3 clinical trial publications. ² The sponsor should provide data to substantiate indication, clinical use, and efficacy in the patient population or dosage regimen to justify ³ When standard treatment/supportive drugs used in dose or schedule not approved by Health Canada and for which no robust supportive data (recognized guidelines, marketing approvals in other regions etc.) are available, or in patient populations likely to have significantly different outcomes (e.g. hepatic cancer)	

For Category B trials, even when a CTA must be filed (for relevant Investigational Product), significant reduction in complexity and costs can be achieved following the principles of OECD by including specific provisions in the trial protocol for:

- Waiving the expedited reporting of some types of foreseeable adverse events to sponsors (see below)
- Limiting the collection of adverse event and concomitant medications data
- Ensuring IP supplied as standard-of-care, using commercial product and following standard pharmacy dispensing requirements (see section 4)

ISCT Recommendations

- Ensuring monitoring and inspection are conducted in a risk proportionate manner. Developing Quality management plans should focus on mitigating key risks (see section 5).

c) Safety Reporting

The *expedited* (i.e. immediate reporting) collection, evaluation and reporting of serious adverse events (SAEs) to sponsors and the subsequent evaluation of suspected and unexpected (i.e. not described in the product monograph/investigator brochure) SAEs (SUSARS) by academic and cooperative group sponsors, can be a major burden for participating sites, and, in turn, for sponsors to review, filter and then submit just a small percentage of these to Health Canada. It is important that the sponsor clearly identifies this in the protocol.

- Which SAEs should be reported to the sponsor in an expedited fashion? For Category B trials, and low risk Category C trials, only drug related and unexpected events that are serious should be reported in an expedited fashion. Other SAEs should be collected on the case record form (CRF) using normal data submission timelines. If this strategy is used, the protocol or trial website must clearly identify which AEs are considered expected (and therefore do not need to be submitted).
- Which adverse events (AEs) should be collected and reported? For Category B and low risk Category C trials, it is appropriate to collect only AEs of interest, which may be those that are higher grade (moderate/severe or grade 3/4 in severity), those that are treatment emergent (excluding symptoms of the underlying disease for example pain in cancer patients), or those of special interest to the drug under study (e.g. cardiac events).

d) Recommendations for CTA Requirements and Safety Reporting

Feasible

- i. OECD framework and recommendations should be adopted and implemented in Canada within the existing regulatory framework.
- ii. Long established drugs or supportive therapies used as the standard-of-care in a clinical trial do not need to be included in a CTA (note that a CTA may be filed for a true Investigational Product used in the same protocol) providing that the sponsor develops specific written justification based on marketing authorizations, Provincial Formularies, systematic reviews, recognized clinical practice guidelines, or robust phase 3 clinical trial publications, and the marketing authorization or international usage is sufficiently broad to allow such interpretation (e.g. cisplatin). These standard-of-care drugs are then considered Category A; trials that include only Category A drugs are then Category A trials with no requirement for CTA filing (see below for notes on less well established drugs or drugs used in special populations such as pediatrics).
- iii. For each proposed trial the investigator/sponsor should carefully consider, and provide justification for, deciding whether a trial and the drugs being used in the trial are Category A, B or C and whether the drug is IP or standard treatment.

ISCT action: develop and provide sample documentation

- iv. Academic trials of low risk should be considered as Category A where justified and within the guidelines. Low, medium and high-risk trials should be prospectively and clearly defined so that consistent interpretations are possible.

ISCT action: develop and provide sample documentation

- v. A database of such trials and decisions should be maintained by Health Canada to ensure consistency and allow for precedent.

ISCT Recommendations

- vi. A joint academia-regulatory initiative is recommended where consensus interpretations can be made (for example, a committee of interested participants)
- vii. Even if a CTA is filed for Category B (and possibly C) trials or drugs, the protocol should ensure that only risk-based, relevant and justified processes for safety reporting and concomitant medication collection are planned and are clearly defined based on the risk benefit profile of the drug and the patient population. Expedited reporting/collection of serious adverse events to the sponsor should be limited to related and unexpected events, and consideration given to collecting only adverse events, and grade/severity of events, of interest.

ISCT action: develop and provide sample documentation

Recommended

- viii. Drugs used in special populations such as pediatric trials or rare tumours, used as the standard-of-care in a clinical trial, remain a major issue. Consideration should be given to amending the regulations so that drugs can be considered as Category A, providing that the sponsor develops specific written justification based on marketing authorizations, Provincial Formularies, systematic reviews, recognized clinical practice guidelines or robust phase 3 clinical trial publications. Those standard-of-care drugs could then be considered Category A, and trials that include only Category A drugs, to be Category A trials with no requirement for CTA filing.

4. Drug Accountability and Labeling

a) Background and identified issues

All pharmacies and pharmacists in Canada are subject to oversight by provincially based Pharmacy Practice Regulations, Pharmacy Acts and professional bodies (Colleges of Pharmacists and the National Association of Pharmacy Regulatory Authorities). These encompass such areas as qualification, continuing education, registration, delegation, dispensing, product integrity (including expiry date management and recall), security, and quality assurance. This oversight ensures the safety of all Canadians. All registered pharmacists and pharmacies must comply with these requirements for all activities. The discussion below encompasses those requirements (referred to as 'Standard Pharmacy Practice'), but in addition refers to Food and Drug Act regulations and guidelines for clinical trials.

Current interpretation of Division 5 regulations and guidelines requires commercially available drug to be managed as if the drug were investigational when used in a clinical trial and when a CTA has been filed for that drug, especially if supplied in some manner even if only to facilitate conduct of the study (for e.g. costs to patients/participants). The requirement for GMP level repackaging and labeling as well as the requirement for accountability procedures significantly increases the cost and complexity of academic trials.

OECD recommendations clarify that for Category A and B trials, drug supply and management can be simplified, in keeping with the use of a marketed product, even if a CTA has been filed. Specifically:

- Commercial product can be used without trial specific labeling
- Pharmacy and pharmacists can repack/label if required (e.g. to facilitate blinding of a clinical trial) adhering to Standard Pharmacy Practices, without adhering to GMP requirements
- Product monographs can be used rather than an Investigator Brochure.

Areas such as drug accountability and the maintenance of clinical trial specific drug accountability logs require further interpretation. ISCT consider the following appropriate:

- Category A trials/drug. Commercial stock, not considered investigational (purchased or supplied) can be dispensed from/by an accredited pharmacy, pharmacist or physician or appropriately delegated individual (ICH E6 4.6.1) with no additional mandatory trial specific requirements such as maintenance of trial specific accountability logs. Shipping, storage, lot numbers, expiry dates and destruction records for commercial stock should be maintained in compliance with institutional, provincial and national policies, identified by pharmacy regulatory bodies. There however may be instances where the trial design may require the use of trial specific drug accountability logs such as for reimbursement purposes or when blinded drug/placebo is used
- For category B trials, IP for *which the CTA was filed*
 - Commercial stock (purchased or supplied) can be dispensed from/by an accredited pharmacy, pharmacist or physician or appropriately delegated individual (ICH E6 4.6.1) with no additional mandatory trial specific requirements such as maintenance of trial specific accountability logs. Shipping, storage, lot numbers expiry dates and destruction records for commercial drug should be maintained in compliance with institutional, provincial and national policies identified by pharmacy regulatory bodies. If commercial drug is dispensed from an accredited community pharmacy but that pharmacy does not retain lot numbers/ expiry dates for an appropriate period of time, then the sponsor could ensure that copies of the prescription are submitted and retain those (e.g. which generic version of the drug (if applicable), lot number, expiry date). There however may be instances

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where the trial design may require the use of trial specific drug accountability logs such as for reimbursement purposes

- Commercial or trial stock which is *labeled as clinical trial supply* can be dispensed/provided to patients from a pharmacy or other acceptable facility but a trial specific accountability log should be maintained. Shipping, storage and destruction records should be maintained as per standard pharmacy practice
- Where standard pharmacy practice is appropriate (for Category A and B trials as described above), the sponsor should develop and institute minimal monitoring processes where appropriate, for example where drug is supplied and contracts or agreements require that the drug be used only in a particular clinical trial
- Category C trials, or IP, should be managed according to GCP, GMP and other applicable regulations and guidelines

b) Recommendations

Feasible

- i. Drugs used in a clinical trial, but for which a CTA has not been filed (Category A trials), should be managed as commercial drugs and standard pharmacy/dispensing practices/policies followed.
- ii. Category B drugs which are commercially available, but for which a CTA has been filed, should be managed as commercial drugs and standard pharmacy practice followed; trial-specific drug accountability logs are required *only* for drugs specifically labeled as clinical trial supply. For such trials, the sponsor should ensure that compliance can be assured (e.g. for oral drugs) and that processes are in place for recall/complaint if needed (e.g. by ensuring that lot numbers are recorded).
ISCT action: develop and provide sample documentation
- iii. On-site monitoring of drug/pharmacy is rarely required for category A and B trials where commercial stock is used.

5. Monitoring

a) Background and identified issues

Regulations require that the sponsor ensure that clinical trials are adequately monitored, and determine the appropriate extent and nature of monitoring. Monitoring plans or models should be created and should consider the objective, purpose, design, complexity, blinding, size, and endpoints of the trial in order to facilitate compliance. OECD recommendations emphasize that quality management plans should focus on mitigating key risks and that inspections, audits and monitoring should be established in a manner that is proportionate to the risk stratification and trial-specific assessment.

Guidance regarding the frequency and scope of monitoring required has not been explicitly defined and, as risk-averse commercial entities have come to dominate clinical research, frequent visits to each site and 100% source data verification remain the predominant mechanism of monitoring for the pharmaceutical industry, although recent initiatives have sought to rationalize this approach.

<http://www.transceleratebiopharmainc.org/content/risk-based-monitoring-methodology-position-paper>

On-site monitoring programs are costly and complex, especially in countries such as Canada with a large geographical distribution of clinical sites. Academic researchers have been required to develop, institute or expand existing programs for trials conducted under a CTA.

Current approaches to monitoring for academic clinical trials in Canada generally include a combination of centralized and on-site monitoring (OSM) as well as audits (see Section 13 for definitions), but rarely include 100% on-site monitoring. While the model used is often risk-based, monitoring for category B and C trials is invariably more than the academic researcher/group feels necessary based on quality metrics, but has been guided by current Health Canada inspectorate interpretation. Of note, academic cooperative group sponsors, or even investigator led trials, may have knowledge of past history and performance within a network of collaborations, which may increase or decrease the need for monitoring at a site level.

Program Models	Centralized Monitoring ¹	On-Site Monitoring ²
1	Selected critical elements	100% for 100% of patients
2	Selected critical elements	Reduced OSM; Sample for 10% of patients
3	Selected critical elements	No OSM

¹ Central review may be systematic via data collected or via de-identified source obtained for review.

² On-Site reviews may be done by trained in-house Investigator/Sponsor team, a sub-contracted third party (i.e. CRO), or may be peer-to-peer within an Institution or across Institutions.

Examples of Monitoring Plans for Academic Trials in Canada

Centralized monitoring can fulfill many of the functions of on-site monitoring, including source data verification (from submitted de-identified copies of source data), site performance and quality evaluation. Central monitoring can use data entry validation and range checks as well as statistical (e.g. SAS) and manual reviews. There is some evidence to suggest that data submission rates are improved when Electronic Data Capture (EDC) systems are used. NCIC CTG noted that for 2012 across all trials, data submission for EDC trials was 88% on time versus 84% for paper trials. Baigent (4) suggests that for large-scale trials with blinded treatments and endpoints involving little risk of misdiagnosis, it may be possible to design procedures that allow central review of data to be the main or only form of monitoring. Venet (5) suggests that central statistical

ISCT Recommendations

monitoring may reveal data issues that had remained undiscovered after careful source data verification and on-site checks due to the systematic approach allowing for the detection of trends in the data. In a clinical trial conducted in patients with HIV by the UK Medical Research Council, on-site monitoring findings were reviewed and of the 268 on-site monitoring findings 76 (28%) were also identified in the central database and 179 (67%) could have been identified through centralized checking. Only 13 (5%) were noted to have only been found via on-site review.

As part of the ISCT development process, a review of data generated by one of the Stakeholders, during on-site monitoring for trials conducted under a CTA, between 2005 and 2012 by was conducted. There was no statistical difference found in on-site monitoring findings between trials that were 100% and 10% source data verified (all were centrally monitored).

Comparison of On-Site Monitoring Processes for the Average Number of Deficiencies Per Monitored Patient

Deficiency Type	On-Site Monitoring 100% Intensive ¹	On-Site Monitoring 10% Standard ²	p value
Major	0.2	0.2	0.13
Lesser	1.2	1.3	0.20
N of Trials	3	37	

¹ On-Site Monitoring Intensive: Central data review through de-identified source documents; On-Site Monitoring of 100% of patient cases and 100% of source data; Percentage based on-site audit.

² On-Site Monitoring Standard: Central data review through de-identified source documents; On-Site Monitoring of a minimum of 10% of patient cases per trial per center; Percentage based on-site audit may be conducted.

b) Developing monitoring strategies

The ISCT recognizes the need to develop a monitoring strategy for each trial as the monitoring approach for one trial may not be appropriate or necessary for another. The monitoring strategy should be determined by the sponsor as part of the risk assessment of the clinical trial. Category A and B trials are ideally suited to central monitoring with very limited (or no) on-site monitoring, congruent with OECD recommendations, as are lower risk Category C trials.

The monitoring strategy should be created and specified in the protocol, referring to a formal monitoring plan or a standard operating procedure. The plan should detail:

- Drug accountability (if applicable, see section 4), and whether this is monitored centrally (e.g. by submitted documentation) or on-site
- Critical study parameters (objectives, outcomes and safety data) and identification of deviations and an acceptable level of variation/ error, as well as actions to be taken if unacceptable
- Identification of the critical data elements (CDE) and the acceptable level of data quality associated with each element. The percentage of CDEs requiring source data verification (on- site or central) should be specified
- Use of statistical analyses to identify trends in data within a site and across all sites to identify potential problems that may necessitate an on-site visit

ISCT Recommendations

- Management of findings that may impose a significant risk to the study participant or the integrity of the data
- Planned on-site monitoring and auditing; under what circumstances this would be increased (e.g. with identified issues) or decreased (e.g. if a certain level of quality is routinely achieved)
- The definition of the frequency and percentage of sites and cases to be reviewed should factor in the risk category (A, B, C). While limited frequency and percentage of sites and cases reviewed may be possible for Category B and some Category C trials, high-risk trials may require higher levels of review. Generally, limited frequency and percentage of sites and cases reviews (i.e. 1-5%) for Category B and most Category C trials is recommended.

c) Recommendations

Feasible

- i. The ISCT Working Group is in agreement with recommendations of the FDA and the OECD with respect to implementation of a risk-based approach to monitoring
- ii. Central monitoring of *selected critical* study parameters and data elements should be the primary strategy for academic trials.
- iii. Limited on-site monitoring may be appropriate for higher-risk Category B trials and for some Category C trials. In general, more intensive on-site monitoring should be reserved for very high-risk trials. The monitoring plan should allow for an increase or decrease in monitoring strategy for one or multiple sites, depending on deviations or data trends identified throughout the course of the trial.

ISCT action: develop and provide sample documentation

- iv. The sponsor should develop robust detailed prospective monitoring plans which are risk-based and can be tailored to findings. These plans should be carefully justified, and summarized in the protocol, or as an Appendix, so that Health Canada can review and hopefully approve it during the CTA review process. Inspectors should review the conduct of studies during inspections based on the agreed monitoring plan for the trial to ensure consistency of interpretation. ISCT feels strongly that the CTA review period is the appropriate time to identify any concerns Health Canada may have with the proposed monitoring plan, as this is a time when change can be effected most easily. ISCT intends to develop sample risk-based monitoring plans and examples to facilitate these recommendations.

ISCT action: develop and provide sample documentation

6. Equipment and Facilities

a) Background and identified issues

The oversight and monitoring of equipment and facilities was identified as a major issue by all participating ISCT members. Health Canada inspections have not differentiated between standard-of-care versus research equipment. Health Canada Inspectors have required documentation of preventative maintenance and calibration for all equipment used to support the conduct of a clinical trial that may have come into contact with a clinical trial subject; from weigh scales and thermometers, to chemotherapy infusion pumps, to MRI and PET scans; without differentiating whether the equipment is related to the delivery of standard-of-care or for the purposes of the clinical trial. This perceived requirement to oversee standard care equipment in clinical trials has significantly impacted the costs and burden of academic clinical trials in Canada.

There is no known established standard adopted by Health Canada to provide guidance or interpretation of the Regulations as it relates to equipment and facilities. The Health Canada Food and Drug Regulations (C.05.010) indicate *that every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that systems and procedures that assure the quality of every aspect of the clinical trial are implemented*. Similarly, GCP Section 5.1.1. indicates that *the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements and section 5.1.3 indicates that quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly*. The Inspectorate provides limited guidance to sponsors in their Pre Inspection Package. Section 4.0 of the document notes that *“Records of calibration, maintenance, and temperature monitoring for the applicable research equipment” should be made available during inspection. This includes calibration and maintenance of equipment*”. Another major issue for monitors, auditors and inspectors, is the lack of technical expertise to be able to appropriately evaluate the equipment maintenance processes, especially for applied technology.

Despite this, Health Canada Inspectors commonly assign deficiencies during inspections of clinical trials that pertain to equipment and facilities citing “documentation or implementation of systems and procedures that ensure the quality of every aspect of the clinical trial and the lack of appropriate record retention” C.05.010 (c) as the standard.

More than 25% of observations made during inspections occurring between 2004 and 2011 referenced C.05.010 (c) (6). It appears as though the lack of an established standard to provide guidance or interpretation of the Regulations as it relates to equipment and facilities has resulted in the C.05.010 (c) being used as a “catch-all” for observations related to equipment and facilities.

The following are examples of observations related to equipment and facilities:

- “There was no system in place to ensure that the laboratory equipment and refrigerators, for blood samples, would be subject to routine maintenance and calibration.”
- “There was no consistency in the process followed to approve/review the validation of the Pneumatic Tube System.”
- “It was noted that a number of devices used in the conduct of the trial were not calibrated and/or maintained. For example, the CT scanners and Gamma Cameras in Medical Imaging.”

During inspections, Qualified Investigators/Sponsors have been requested to provide a variety of calibration records relating to equipment and facilities; including records (e.g. a documented process, maintenance schedules, Operation/User Manuals, service contracts for external vendors, and records and proof of documented evidence of routine/annual calibration) pertaining to equipment ranging from thermometers to

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chemotherapy infusion pumps to MRI and PET scans. During the corrective action process academic sites have been required to put in place supernumerary processes (i.e. over and above the existing institutional processes) incurring significant costs, and in some instances have had to purchase or acquire new equipment, or require examinations to be done in certain sections of the clinic. Some sites are now requiring collaborating sponsors to provide new calibrated equipment before they will participate in a trial.

There are significant complexities associated with limiting the scope of an additional calibration program to select pieces of equipment used only for patients enrolled in a clinical trial. For example, having a clinic where only two of twenty exam rooms have specially calibrated equipment then requires assurance and documentation that all clinical trials patients will be examined in those two rooms only. This has the potential to cause significant delays with patients and their health care providers having to queue for those rooms when a broad definition of 'research' is applied.

In many instances this has been required for activities which are standard-of-care, and are not related to endpoints of the clinical trial (e.g. thermometers or weight scales).

b) Governance of Clinical Care Related Equipment

There are existing regulations and process in Canada that govern all aspects of clinical care and the equipment used to support delivery of clinical care. This includes, but is not limited to:

- Hospital and laboratory accreditation processes
- Laws and regulations governing the transportation and sale of commercial drugs in Canada
- Radiation safety and employment standards for health professionals (including hospital appointments and medical and nursing licensing procedures).

Many of the current processes that govern hospitals and health care centers in Canada are subject to existing Health Canada, Government of Canada, or provincial regulations which provide appropriate oversight mechanisms. ISCT believes that the mechanism to oversee standard clinical care practices is not the oversight of clinical academic clinical trials.

c) Research versus Standard-of-Care

Regulations define a clinical trial as *“any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.”* From a legal perspective, the term standard-of-care is defined as *“the caution that a reasonable person in similar circumstance would exercise in providing care to a patient.”* (7)

Academic clinical trials commonly include subjects who are patients and are undergoing treatment for their underlying disease (e.g. cancer, diabetes), and rarely includes normal subjects for whom all interactions with health care professionals are truly 'research'. Ensuring a clear understanding of what comprises 'standard-of-care' versus 'research' is a critical element of the care of any patient considering participating on a clinical trial, as it directs the informed consent process, complexity and added inconvenience for the subject, as well as budgeting and resource considerations. Almost always, academic clinical trial sponsors will ensure that the protocol confirms as closely as possible to standard-of-care pathways to minimize cost and complexity, but also to ensure generalizability of the results.

Unfortunately, the interpretation of the scope of research versus standard-of-care with respect to the Regulations and guidelines pertaining to equipment used to support a clinical trial has led to a focus, as noted above, on calibration and maintenance of institutional equipment used for the care of all patients, rather than on aspects of the clinical trial that are truly “research”. Although the ISCT recognizes that some areas are

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difficult to categorize, and that the delivery of high quality patient care is critical for all Canadians, other processes such as accreditation of institutions should be the preferred route of assuring such quality, rather than the academic clinical trials process. The convergence of the two perspectives leads to the ISCT recommendation that the term “research equipment” for clinical trials be defined as equipment used solely for the purpose of a clinical trial and unrelated to the delivery of standard-of-care.

Standard-of-care applies to many aspects of patient management, examples of which include assessment of response to therapy, measurement of PSA levels, assessment and collection of vitals, as well as height and weight measurements. Subjects undergo these procedures irrespective of their participation on a clinical trial. The responsibility for calibration or maintenance of equipment pertinent to standard-of-care rests with the host institution responsible for providing health care. Institutions are able to provide accreditation certificates or letters confirming compliance with general Canadian laws, regulations and requirements as opposed to research based requirements (i.e. Food and Drug Regulations Part C Division 5).

Research specific activities (non-standard-of-care) include aspects such as correlative laboratory sampling and storage, and pharmacokinetic sampling. An important consideration in defining research versus standard-of-care procedures is based on risk, where later clinical trials of agents with a well-documented safety profile require fewer non-standard investigations.

d) Maintenance

Equipment maintenance encompasses both preventative maintenance and calibration of equipment and is a continuum.

Calibration is *“a set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards”*

Preventative maintenance requires *“the institution (Qualified Investigator/Sponsor) to determine, provide, and maintain the infrastructure needed to achieve conformity to product requirements which includes process equipment”*, and requires the maintenance of equipment or systems before fault occurs to keep equipment working and/or extend the life of the equipment.

Most institutions focus on preventative maintenance procedures to ensure the equipment is functioning as intended per the manufacturer’s specifications. Equipment maintenance programs at institutions usually consist of the manufacturer’s Operator/User manual as well as the Standard Operating Procedures (SOPs) relating to equipment maintenance for the institution. Records should contain documentation of oversight and surveillance of the equipment maintenance process through the use of tools such as equipment catalogues and performance verification logs. Additional recommendations for equipment maintenance such as frequency, records and retention, training, and responsibilities are detailed in Network of Network (N2) Equipment Maintenance Guidance and Standard Operating Procedure. (8)

e) Risk-Based Equipment Maintenance Process

The maintenance requirements for all equipment, irrespective of whether used to support the delivery of standard-of-care (and thus the responsibility of the institution) or used for the purposes of the clinical trial should be determined according to standard algorithms. First and foremost, safety of patients including those involved in clinical trials must be ensured. For research equipment, risk and importance of the endpoint is an essential consideration in identifying the appropriate process to follow. For example, infusion pumps are commonly used to administer intravenous chemotherapy for oncology patients, but the rationale for such use is varied; in some instances, the chemotherapy drug can be safely administered, without changes in outcomes, over a wide time period (e.g. 1-60 minutes) but is given with an infusion pump for convenience and efficiency.

ISCT Recommendations

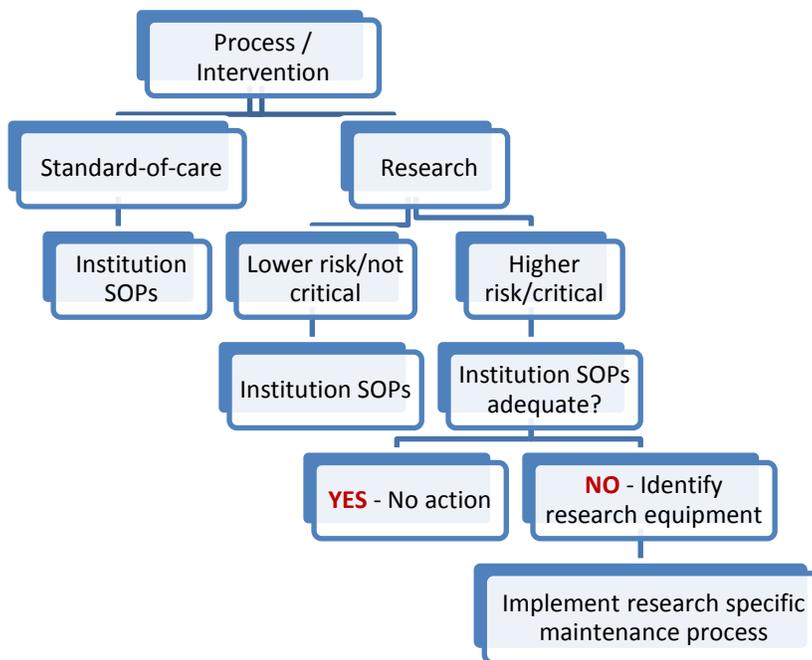
In other instances, for example in a phase I trial, the accurate identification of infusion rates and timing is critical to the understanding and interpretation of the trial. Therefore, different levels of maintenance requirements may be appropriate even within clinical trials.

Factors to consider when determining the appropriate equipment maintenance process for research equipment include:

- Type of equipment
- Risk to patient
- Existing oversight process (i.e. hospital, laboratory, or other accreditation process)
- Operating Manual / manufacturer specifications for equipment
- Existing institutional Standard Operating Procedures for equipment maintenance

Following this assessment, the need for equipment maintenance including preventative maintenance, routine calibration, or both, should be documented. Once defined, other requirements for equipment maintenance and guidance should be implemented as described below.

Suggested Algorithm for Defining Critical Research Equipment



f) The Protocol and Data Collection

Based on the definition of the term “research equipment”, and separation of oversight of research activities versus standard-of-care, it is further recommended that research protocols clearly define the research activities so that appropriate Quality Assurance/Control processes can be planned (see Section 5). Collection of general standard-of-care data points (i.e. vitals) should not be included in protocols unless critical to the study endpoint.

g) Recommendations

Feasible

- i. The ISCT recommends that the term “research equipment” for clinical trials be defined as equipment used solely for the purpose of a clinical trial and unrelated to the delivery of standard-of-care.
- ii. The ISCT recommends that the responsibility for maintenance and calibration of equipment associated with standard-of-care delivery rests with the Institution.

ISCT Recommendations

- iii. The ISCT recommends that the management of equipment for research specific activities include an assessment of risk and acceptability of institutional programs prior to implementing a trial specific equipment maintenance process.
- iv. The ISCT recommends that the requirements for maintenance of equipment designated as research be documented appropriately and prospectively in the protocol or an appendix and that Inspectors use that agreed plan when conducting site inspections.

ISCT action: develop and provide sample documentation

7. Delegation of Significant Trial Related Duties

a) Background and Identified Issues

Clinical trials in Canada are conducted in a variety of settings (e.g. acute, outpatient, family practice clinic, research centers, community centers, in a variety of locations (urban, rural, remote) and examine a variety of clinical questions. The Qualified Investigator (QI) is a qualified health care professional, according to the Health Canada, Regulations Amending the Food and Drug Regulations, Division 5, restricted to physicians and dentists (for studies of dental drugs), who is responsible for ensuring there is an adequate number of staff, and that staff are qualified and trained to perform the duties they are delegated, as required by the study protocol. The QI must sign a Qualified Investigator Undertaking (QIU) form, which states that the QI will “supervise the medical care and medical decisions respecting this clinical trial at this site”.

Although regulatory guidelines have remained vague regarding delegation of duties it has resulted in inconsistent implementation of the guidelines. Current regulations do not specify the training or education required for performing any task related to clinical trial conduct, other than qualifications of the QI. As a result, QIs have been questioned by sponsors and health authorities regarding the appropriateness of the delegation of certain study activities, including the following findings:

- Inspectors and auditors have indicated that there are certain activities that should not be delegated to non-physician staff members, and further, that ‘training’ is not always adequate.
- In some instances, curriculum vitae are requested for all staff, even hospital employees performing standard-of-care procedures.
- Similarly, sites are requested to add all employees to participants lists even if they, for example, examine the patient during an unplanned emergency room visit
- Although not clearly stated in any regulation, inspection and audit findings suggest there is a perceived process for delegation of activities and that this is a very precise process requiring specific detail (e.g. start date on project, role, specific detail on type of assessment provided).

b) Inspection Findings

The following summarizes some of the findings from the Health Products and Food Branch Inspectorate’s Summary Report of Inspection of Clinical Trials Conducted, April 2004 to March 2011 (issued March 28, 2012) regarding issues around delegation of duties and inadequate qualifications, education and training of personnel:

- There was no documented evidence that the personnel, including study coordinators, at all sites involved in the conduct of the study were trained on the protocol, good clinical practices and regulatory requirements.
- There was no explicit documentation to indicate that all sub-investigators and nurses to whom significant trial-related duties have been delegated had been informed of all protocol-specific requirements.
- Documentation was lacking to show the delegation of the task of “drug administration” to study staff that performed this activity
- The delegation log was deficient as there was no provision for the Qualified Investigator (QI) to date his/her signature.

c) Recommendations

Feasible

ISCT Recommendations

- i. Roles required as part of standard-of-care, or as part of care provided on an *ad hoc* basis, are not required to be documented as part of the trial delegation log (e.g. imaging, emergency room staff).

ISCT action: develop and provide sample documentation

- ii. If a specific trial-related task requires a level of training beyond the usual scope of practice, or requires a specific professional to conduct the task, it will be stated in the protocol or in the operational documentation from the study sponsor.

ISCT action: develop and provide sample documentation

- iii. Otherwise, tasks can be delegated by the QI to an individual qualified to perform that task or process, and no additional training (other than study specific training) is required.
- iv. The delegation list, either the initial list or any modified version, will be created and maintained by the QI, or delegate, in a timely manner. Verbal authorization from the QI to begin a trial-related task is permissible, with the delegation log to be revised within an acceptable window, to be determined and prespecified by the sponsor. Sign-off of each change to the delegation list by the QI is not required if the task is delegated appropriately.

ISCT action: develop and provide sample documentation

- v. CVs and other documentation (e.g. financial disclosures) are only required for the QI and sub-investigators, provided that other staff, who are delegated tasks, are employees of the institution.

8. Validation of Electronic Systems

a) Background and identified issues

The use of Electronic Data Capture (EDC) systems continues to proliferate in clinical trials. Electronic systems are also used to control critical trial related activities including: randomization, study drug assignment, study drug expiry date management, and “breaking the blind”.

Across all regulations and guidelines, the primary objective of the validation of electronic system include is to ensure that records collected or generated throughout the study are acceptable as trustworthy and reliable.

b) ISCT Recommendations for Validation of Electronic Systems

Feasible

- i. An electronic system used as the permanent record for regulatory purposes needs to be validated for its intended use and records retained in accordance with the Regulations. Processes of the software development and deployment need to align with Software Development and System Operation Good Practices, and be appropriately documented.
- ii. The level of validation of the electronic system needs to be consistent with complexity, level of customization, and overall risk assessed.
- iii. Requirements and Policies related to the retention of records need to align with Institutional Policies where applicable.

9. Source Documents and Document Retention

a) Background and identified issues

The retention of clinical trial documentation and source documents is an essential ingredient in the verification of who, what, when, where and how a clinical trial was conducted. It is also well recognized that this verification may need to occur many years after the conclusion of the trial. However, the current requirement for retention of records at Canadian sites, as dictated by Division 5, is 25 years. Since its inception in 2001, this requirement has been significantly out of step with other regulatory agency requirements for retention of records, which creates additional hurdles for Canadian sponsors and sites in the competitive international arena (see section 14 Table 3). The retention of records period should be limited to a time period consistent with other regulatory agencies.

The Health Products and Food Branch Inspectorate's Summary Report of Inspection of Clinical Trials Conducted from April 2004 to March 2011 (issued March 28, 2012) states "observations relating to the accuracy and adequate maintenance of records constituted 25.4% of all observations". Examples include "*There was no assurance that electronic records would be maintained for the required period of 25 years. Although a procedure on record retention was in place, electronic records were not addressed. Further hospital charts/records considered to be source documents were not addressed for archiving purposes of 25 years.*"

b) Challenges in the Canadian Environment

- Procedures for local review of source documentation vary greatly, resulting in questions about how/when key study documents (e.g. laboratory reports) have been reviewed by the appropriate study personnel
- Retention period for Canada is in excess of any need for document review by approximately 10 years.
- Requirements for health record retention are shorter (e.g. 10 years in Ontario from date of record creation) therefore source documents may be destroyed without extraordinary efforts being made to keep these documents. Given the nature and ownership of the e-health records it is not reasonable to expect the QI to make provisions to keep the source data in electronic form.
- If the intent of accessing source data is to determine whether participants are "real", study related documents cannot provide the required authentication.
- Limited data require validation; however the scope of data validation is not limited in an audit.
- When data validation is required it should be done against a reliable and original source and therefore requirements for transcription of data are not appropriate to meet the objective.
- The term source document may no longer be applicable given that source data may exist independently in an electronic format. The availability of source data in other forms must be taken into consideration.

c) Recommendations

Feasible

- i. Source document review: For documentation identified as requiring a review in the protocol, there should be a record that either the QI or sub-investigator has reviewed the protocol-defined out-of-range results.

ISCT action: develop and provide sample documentation

- ii. The protocol should identify those data elements requiring source documentation, and sites can then declare the type of source documents (e.g. chart-based, e-record, a combination).

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- iii. Investigators are not required to store electronic CRFs (eCRFs) after study completion if data have been collected through an electronic database. The sponsor will store these data.

Recommended

- iv. Record retention policies will be according to institutional policies. If the trial data are being used to support a marketing application, once all data are collected and quality assurance policies completed, on-site data storage need only follow institutional policies. The sponsor will keep these data for 10 years after marketing application submission. This will require a change to the Food and Drug Act.

10. Trial costs

a) Background and identified issues

The cost of conducting Investigator Initiated Studies in Canada continues to rise. These increased costs are attributed to many factors including increased bureaucracy, poor trial completion rates, increasing administrative costs, excessive regulation and regulatory compliance (9).

Regulations governing the conduct of clinical trials are necessary to provide guidance for the conduct of clinical trials; however the system has become unnecessarily complex and expensive. There are examples throughout this document about well-intended regulations that have resulted in increased amounts of effort and administrative paperwork with little to no measureable positive impact on the ethical conduct of clinical research. Decreasing the number of studies requiring CTAs will decrease regulatory compliance burden. It is also clear that the interpretation of these regulations can result in dramatically increased clinical trial costs. In the past 10 years the NCIC Clinical Trials Group has increased staffing dedicated to regulatory compliance from 7% of their workforce to nearly 22% while overall enrollment in their studies has decreased by about 17% indicating an increased regulatory compliance burden.

Impact of Changing Regulations and Requirements on Resource



Pharmacies must maintain drug accountability records for commercial supplies. Pharmacies and other hospital units have initiated start-up and maintenance fees aimed at recovering costs related to increased regulatory compliance. For Investigator Initiated Studies that utilize commercial supply as the study medication elimination of the additional drug accountability record keeping will decrease the regulatory burden and as a consequence decrease study costs.

On-site monitoring has considerable cost implications for clinical trials. The adoption of a risk-based monitoring approach allows for the limited resources available to be targeted to studies that would benefit from increased site monitoring.

For Investigator Initiated Studies, there are no additional financial resources available for these increased regulatory compliance costs resulting in fewer studies being conducted.

The costs of conducting Health Canada regulated academic clinical trials use a significant portion of funding for clinical trials conducted in Canada, irrespective of the source of the funding. The Canadian Institutes of Health Research (CIHR) funds many of these clinical trials conducted in Canada and internationally. Research funding available from the Canadian Institutes of Health Research, the primary federal government research funding agency, to conduct Investigator initiated studies classifies as non-eligible expenses which are necessary to comply with Health Canada regulations. Through their published Use of Grant Funds guidelines, CIHR specifically excludes certain expenses necessary for the safe and Health Canada compliant conduct of clinical trials. This includes expenses associated with, "Costs associated with regulatory compliance, including

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ethical review, biohazard or radiation safety, environmental assessments, or provincial or municipal regulations and by-laws.” While not mentioned in the guidelines, upon inquiry to CIHR clinical trial insurance is also deemed a non-eligible expense.

b) Recommendation:

Feasible

- i. CIHR funding guidelines and eligible expenses for clinical trials conducted under a Health Canada CTA must be aligned with Health Canada regulations to allow for the payment of essential expenses related to regulatory compliance. This would include regulatory support for CTA submissions, study monitoring and oversight activities, research ethics board fees, and clinical trial insurance.

11. Other

a) Background and identified issues

The primary stated role of the Health Products and Food Branch Inspectorate is to deliver a national compliance and enforcement program for products under the mandate of HPFB. From the website the "*inspectorate is responsible for the management of a **consistent branch-wide** approach to compliance...*" and "*... follow(s) a predictable uniform and national approach to enforcement in Canada for all of HPFB regulated products irrespective of where or by whom these products are sold, advertised fabricated processed package/labelled, imported, distributed, tested or stored*".

Stakeholders agree that compliance is facilitated when legislation and regulatory requirements are clearly understood. Challenges exist for the research community when there is inconsistency between regulations, inspections and inspectors.

Compliance can sometimes seem to be a moving target less driven by the legislation than the individual. Shared experiences between ISCT members have demonstrated that what was acceptable for one inspector has not always been acceptable with another inspector. The academic community shares experiences and may make process changes that may not be necessary or even not be acceptable to other inspectors. Many sites across Canada are experiencing this inconsistency which includes areas such as:

- Focus on standard-of-care equipment calibration,
- Delegation of activities
- Evidence of adequate training on the protocol, amendments, or HC division 5.

Other observations include delays in responses from Health Canada with respect to review and approval of submitted corrective action plans. ISCT members have reported it taking up to 10.5 months to obtain a response. Delays mean sites may be taking inappropriate actions - and expend time, resource and funding but continue to be non-compliant. Some sites have reported having a subsequent inspection while waiting for a response to the first.

Many end-users report that the Health Canada website is difficult to navigate, lacking a site map specifically for Clinical Trials. Search functions do not work well and may link to inappropriate (and often dated) information. In addition Qualified Sponsor-investigators, institutions acting as sponsors and academic cooperative groups sponsoring studies especially those who have not conducted large numbers of CTA trials, frequently find the process and communication bewildering. The current system, with multiple Directorates, different addresses, contact people and fax numbers, different reporting mechanisms such as fax and email can be challenging to follow. A streamlined approach, perhaps with single point of entry, as well as electronic submissions would help manage these.

b) Discussion and Suggestions

Feasible

Inspection Preparation

- For academic trials a simple, short standard questionnaire for the site to complete prior to an inspection would provide some context to the inspector on how the site operates (i.e. do other facilities participate in the research process).

ISCT action: develop and provide sample documentation

- A more structured approach for inspections, rather than requiring each inspector to individually interpret regulations, would also assist in ensuring more consistency among inspectors

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Post-inspection Communication

- Health Canada might consider a default period for approval of corrective action plans, where approval is understood after a default of 30 days
- A guidance document that outlines acceptable practices, specific to academic trials, with respect to different findings would assist in the development of consistent compliant responses.
- Staff training (i.e. GCP, Division 5, Protocol). Guidance document should be created that sets standard for what is acceptable as evidence of training. ISCT recommends that training can be demonstrated by the following: certificates, CVs, minutes of meetings (with attendance), signed note to files, but that template documents should be provided that includes required sections (date, duration, trainer, agenda, and attendees).

ISCT action: develop and provide sample documentation

- It should be clarified that:
 - People need to be trained only on relevant areas
 - People performing standard-of-care processes (e.g. standard laboratory tests or administering standard –of-care chemotherapy) do not need trial specific training or to be on the delegation list unless the processes are trial specific.

Website

- The Health Canada website could be improved by the inclusion of a site map - specifically for Clinical Trials.
- The addition of an advanced search function would also allow for more appropriate hits.

Recommended

- ISCT recognizes the complexity of organizational structures and processes within the Federal government and Health Canada, and the difficulty with ensuring consistency and efficiency across multiple organizational parts, especially with different reporting structures, which may be regional. Nonetheless, the impact of this on the academic research community is very costly (in terms of both dollars and resources). Clear, simple and consistent processes and interpretation, would significantly improve the access of Canadians to non-commercially driven trials, which have been proven to improve outcomes. This recommendation, in the opinion of ISCT, is critical.

12. References

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13. Glossary

Audit

Per ICH GCP is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsors SOPs, GCP, and the applicable regulatory requirements

Calibration

is *“a set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards”*

Centralized Monitoring

The FDA defines central monitoring as a remote evaluation carried out by sponsor personnel or representatives at a location other than the site(s) at which the clinical investigation is being conducted.

Clinical Trial

The definition of a “clinical trial” in the Food and Drugs Regulations Drugs for Clinical Trials Involving Human Subjects “means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug”.

Drug

“Drug means a drug for human use that is to be tested in a clinical trial”

Qualified Investigator

“qualified investigator” means a person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is:

- a) In the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist...; and
- b) In any other case, a physician...

On-Site Monitoring

Per ICH GCP is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable regulatory requirements.

Preventative maintenance

requires *“the institution (Qualified Investigator/Sponsor) to determine, provide, and maintain the infrastructure needed to achieve conformity to product requirements which includes process equipment”*, and requires the maintenance of equipment or systems before fault occurs to keep equipment working and/or extend the life of the equipment.

Standard of Care

From a legal perspective, the term standard-of-care is defined as “*the caution that a reasonable person in similar circumstance would exercise in providing care to a patient.*” (7)

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14. Tables and Supplementary Materials

a) Table 1: Members of the ISCT

Name	Affiliation
Alison Urton	NCIC Clinical Trials Group
Michelle Filice	Sunnybrook
Jackie Bosch	Population Health Research Institute, McMaster
Jim Pankovich	HIV Network, UBC
Kathy Brodeur-Robb	C17
Marilyn David	Alberta Health Services
Rachel Syme	Alberta Health Services
Karen Arts	Ontario Institute for Cancer Research
Bernhard Eigl	BC Cancer Agency
Donna McCarty	Ontario Clinical Oncology Group, McMaster
Janice Grant	BC Cancer Agency
Jasmine Brown	Princess Margaret Hospital
Jim Julian	Ontario Clinical Oncology Group, McMaster
Lesley Seymour	NCIC Clinical Trials Group
Mirek Piaseczny	HIV Network UBC
Jacqueline Halton	Childrens Hospital of Eastern Ontario
Manisha Thakur	Population Health Research Institute, McMaster

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b) Table 2: Respondents to the Survey

Alberta Health Services	Alberta Children's Hospital	Centre Hospitalier de l'Université de Montréal
C17 Council	C17 Network (pediatric academic centers)	Centre Hospitalier de l'Université de Sherbrooke
Centre for Addiction and Mental Health	Coordinator-UOHS	Credit Valley Hospital
Hôpital du Sacré-Coeur de Montréal, Research Center, Oncology	Hospital for Sick Children	Humber River Regional Hospital
London Health Science Centre/LRCP	McGill University Health Center, Montreal, Canada	McGill University Health Centre
NCIC Clinical Trials Group	Ontario Institute for Cancer Research	Ontario Institute for Cancer Research
Cancer Centre of South East Ontario, Kingston, ON	Pacific Parkinson's Research Centre, University of British Columbia	Pediatric Neurology at the Alberta Children's Hospital
Princess Margaret Hospital	Population Health Research Institute (PHRI)	Jewish General Hospital
Jewish General Hospital	Quality Management in Clinical Research, University of Alberta	Quebec Clinical Research Organization in Cancer
Royal Victoria Regional Health Centre, Barrie, ON	Southlake Regional Health Centre	St. Joseph's Health Centre
Sunnybrook Regional Cancer Centre	The Ottawa Hospital Research Institute (OHRI)	Thunder Bay Regional Health Sciences Centre
Trillium Health Centre site of the Credit Valley Hospital	University of Ottawa	University of British Columbia

Note: some institutions have multiple respondents

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c) Selected Software Development and System Operation Requirements and Good Practices

- Ensure validation (completeness, accuracy, reliability, and consistent intended performance).
- Maintain SOPs for using these systems including
 - Access Control, Security,
 - Backup and Restore,
 - Monitoring etc.
- Train staff in the above SOP and have evidence that training was conducted.
- Ensure that the systems are designed to permit data changes in such a way that
 - Maintain a security system that prevents unauthorized access to the data.
 - Maintain a list of the individuals who are authorized to make data changes.
 - Maintain adequate backup of the data.
 - Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).
 - The data changes are documented and that there is no deletion of entered data (i.e. maintain audit trail, data trail, edit trail).
- Electronic Systems used for clinical trials should be supported by evidence that
 - software specifications conform to user needs and intended uses,
 - The particular requirements implemented through software can be consistently fulfilled. This includes evidence of best practices followed and documented during the entire software life cycle.
- Servers that the electronic system sits on should be qualified and include
 - requirements document
 - installation and configuration document
- When off-the-shelf (OTS), or software as a service (SAS) is used, the following is required
 - documentation of the system validation provided by vendor
 - functional testing of the system.
- When a custom or bespoke system has been developed by an organization, the following is required
 - documentation for system validation
 - user acceptance testing of the system and the documentation of tests.
- Archival storage of the electronic records require
 - copies of records are held in common portable formats,
 - format of archived records is compatible with the concurrently available software.
- The organization should follow a Change Management process that uses a risk assessment approach to determine the level of the validation required.

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d) Table 3: Global Document Retention Requirements

Country	Period of Storage	Requirement	Section	Document
Americas				
<i>Good Clinical Practice (GCP)</i>	2 years	Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.	4.9 Records and Reports, 4.9.5, Page 25	GUIDANCE FOR INDUSTRY Good Clinical Practice: Consolidated Guideline ICH Topic E6, Health Products and Food Branch Guidance Document, Health Canada, 1997
Canada	25 years	The sponsor shall maintain all records referred to in this Division for a period of 25 years.	Food and Drug Regulations, Division 5, Records C.05.012 (4), Page 14, (June 27, 2012)	Clinical Research Reference Guide for Drugs, Devices and Natural Health Products in Canada, Clinical Research Resources, LLC. 2013, Book 11
Argentina	10 years	All the study documents shall be retained for ten years after the date of the last visit of the last patient enrolled in the center.	Section C: Guideline for Good Clinical Practice in Clinical Pharmacology Studies, Essential Documents of the Study, Documents file and retention	National Administration of Drugs, Foods and Medical Devices Regulation 6677/10, A.N.M.A.T., November 1, 2010

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Country	Period of Storage	Requirement	Section	Document
Brazil	5 years	The researcher must ... e) keep in a file, under his/her guard, for five years, all research data, including individual records and all other documents recommended by the CER	IX – Operationalization, IX.2, Page 31	Rules on Research Involving Human Subjects (Res. CNS 196/96 and others), Brasilia, Series E. Health Legislation, 2003
Chile	2 years	The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.	6.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee, 6.5.10, Page 27	Good Clinical Practices: Document of the Americas, Pan American Health Organization
Colombia	2 years	5. The researcher, in agreement with the sponsor, must save the essential documents for at least two years after the last approval of a marketing application or until at least 2 years after formal discontinuation of clinical development of the investigational product. 8. The sponsor must ensure and facilitate the maintenance of essential documents file for at least 2 years.	Table 10. Principal Investigator Functions Relating to the Use of Information, 5., Page 26, &B Table 19. Functions of Sponsor, 8., Page 38	Resolution Number 2378, Good Clinical Practice for Institutions that Conduct Research with Drugs in Humans, Ministry of Social Protection, 2008

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Country	Period of Storage	Requirement	Section	Document
Mexico	2 years	The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.	6.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee, 6.5.10, Page 27	Good Clinical Practices: Document of the Americas, Pan American Health Organization
USA	2 years	<p>Sec. 312.57 (c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.</p> <p>Sec. 312.62 (c) Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.</p>	Code of Federal Regulations, Title 21, Volume 5, Chapter 1, Part 312, Subpart D, Sec. 312.57, Recordkeeping and record retention & Sec. 312.62 Investigator recordkeeping and record retention, (April 1, 2013)	Federal Regulations for Clinical Investigators

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Country	Period of Storage	Requirement	Section	Document
Venezuela	2 years	The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.	6.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee, 6.5.10, Page 27	Good Clinical Practices: Document of the Americas, Pan American Health Organization
Asia-Pacific				
Australia	5 – 15 years	<p>Each institution must have a policy on the retention of materials and research data... The institutional policy must be consistent with practices in the discipline, relevant legislation, codes and guidelines.</p> <p>2.1.1 In general, the minimum recommended period for retention of research data is 5 years from the date of publication. However, in any particular case, the period for which data should be retained should be determined by the specific type of research. For example: ...</p> <ul style="list-style-type: none"> - for most clinical trials, retaining research data for 15 years or more may be necessary 	Part A, Section 2: Management of Research Data and Primary Materials, Responsibilities of Institutions, 2.1 Retain research data and primary materials	Australian Code for the Responsible Conduct of Research, Australian Government, National Health and Medical Research Council, Australian Research Council, 2007

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Country	Period of Storage	Requirement	Section	Document
China	5 years	All data of the clinical trial shall be kept and managed in accordance with regulations (Appendix 2). The investigator shall keep the documents of the clinical trial for five years after the completion of the trial. The sponsor shall keep the clinical trial data for five years after the investigational product has been approved for marketing.	Good Clinical Practice, Chapter 8 Records and Reports, Article 52, Page 11	The People's Republic of China: Selected Laws and Regulations on Drug Research and Good Manufacturing Practice, Clinical Research Resources, 2011, Book 26
India	3 years	It shall be the responsibility of sponsor to make arrangements for safe and secure custody of all study related documents and material for a period of three years after the completion of the study or submission of the data to the regulatory authorities whichever is later.	Guideline for Good Clinical Practice for Clinical Research in India, Responsibilities, 3.1. Sponsor, 3.1.5. h., Page 40	Selected Regulations & Guidance on Good Clinical Practice in India, Clinical Research Resources, 2011, Book 12
Japan	3 years	The sponsor shall appropriately retain the following records (including documents and data) related to the clinical trial until the day on which marketing approval of the test drug is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 24, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later.	Chapter III. Standards for Clinical Trial Management, Section 1, Article 26. Record Keeping - 1., Page 20	Ministerial Ordinance on Good Clinical Practice for Drugs, Last amended by the Ordinance of the Ministry of Health, Labour and Welfare No. 161, December 28, 2012 (Provisional Translation as of March 2013)

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Country	Period of Storage	Requirement	Section	Document
Korea	5 years	The sponsor, or other owners of the data, shall retain all of the sponsor-specific essential documents pertaining to the trial for five years.	Chapter 5. Sponsor, Article 29 (Record Keeping)	Guideline for Korean Good Clinical Practice (unofficial translation version *January 4, 2000), Korea Food & Drug Administration, 1999-67
Philippines	2 years	Adheres to Good Clinical Practice Guidelines.		
Europe				
<i>European Union Directive</i>	5 years	The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.	EU 2001/20/EC, Good Clinical Practice, Chapter 4 The Trial Master File and Archiving, Article 17, Page 8	Selected Regulations & Guidance for Drug Studies, Clinical Research Resources, 2011, Book 1A
Austria	5 years	Adheres to the European Union Directive Regulations & Guidance.		
Belarus	5 years	Adheres to the European Union Directive Regulations & Guidance.		
Croatia	5 years	Adheres to the European Union Directive Regulations & Guidance.		
Denmark	5 years	Adheres to the European Union Directive Regulations & Guidance.		

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Country	Period of Storage	Requirement	Section	Document
Estonia	15 years	<p>(2) The principal investigator shall ensure the preservation of essential information collected in the course of the trial, including some information for at least fifteen years after the end of the trial.</p> <p>(3) The sponsor and the persons conducting the trial shall ensure the preservation of all information concerning the investigational medicinal product for the time of validity of the marketing authorization of the medicinal product or for at least five years after the termination of the use of the medicinal product for research purposes unless the sponsor or his or her representative and the person conducting the trial have agreed otherwise.</p>	11. Collection and storage of data relating to the conducting of trial	Conditions and Procedure for Conducting Clinical Trials of Medicinal Products, Regulation No. 23 of the Minister of Social Affairs, 17 February 2005
Latvia	5 years	<p>92. The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion, except for documents referred to in paragraphs 93 and 94.</p> <p>93. The investigator is responsible for retaining the list of subject identification codes for at least 15 years.</p> <p>94. The sponsor is responsible for retaining the protocol, standard</p>	XII. The Trial Master File and Archiving	Regulations on Clinical Trials, Cabinet Regulation No. 289, 23 March 2010

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Country	Period of Storage	Requirement	Section	Document
		operating procedures, investigator's brochure, case report forms of each subject, clinical trial report, written opinions on the protocol and the progress of the clinical trial for at least five years after the authorization of the investigational product.		
Lithuania	15 years	Researcher and sponsor will store key study documents for a period not less than 15 years after study completion.	XVI. 108.1	DĖL LEIDIMŲ ATLIKTI KLINIKINIUS VAISTINIŲ PREPARATŲ TYRIMUS IŠDAVIMO, TYRIMŲ ATLIKIMO IR KONTROLĖS TVARKOS APRAŠO PATVIRTINIMO (Regarding permission to perform clinical testing of medicinal products for Research Conduct and Control, Description of Procedures), Lithuania Minister of Health, No. 435, May 31 2006
Finland	15 years	The original trial documents must be stored for at least 15 years from the end of the trial.	14. Trial Documentation and its Storage, Page 15	Clinical Trials on Medicinal Products in Human Subjects, National Agency for Medicines, Regulation 1/2007
France	Adheres to the European Union Directive Regulations & Guidance.			
Germany	Adheres to the European Union Directive Regulations & Guidance.			
Hungary	5 years	The sponsor and the investigator must retain basic documents concerning the clinical trial and required for the post-inspection of the	Retention of trial documentation, Section 24, (2)	Clinical Trial and Clinical Practice of Investigational Medical Products, Minister of Health, Decree 35/2005 (VIII).

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Country	Period of Storage	Requirement	Section	Document
		clinical trial for a minimum of five years reckoned from the completion of the trial, and must archive them in a manner allowing for easy retrievability.		26.)
Ireland	5 years	The sponsor and the investigators are required to retain the essential documents relating to a clinical trial for at least five years after its completion.	11. Archiving, Page 16	Guide to Clinical Trial Applications, Irish Medicines Board, 2013
Israel	15 years	The Sponsor/Principal Investigator shall keep all the application documents, including the documents submitted to the Ethics Committee for approval, and all the documents obtained during the clinical trial, for at least 15 years from the completion of the trial.	19. Document retention, 19.2, Page 40	Guidelines for Clinical Trials in Human Subjects, Ministry of Health, Pharmaceutical Administration, Jerusalem, 2006
Italy	Adheres to the European Union Directive Regulations & Guidance.			
Netherlands	Adheres to the European Union Directive Regulations & Guidance.			
Norway	15 years	Sponsor and investigator shall store documents of major significance to the clinical trial for at least fifteen years after the trial is concluded.	Chapter 8 – Documentation (Master File) and final report, Section 8-2. Sponsor's and investigator's storage of documentation	Regulation relating to clinical trials on medicinal products for human use, Norwegian Ministry of Health and Care Services, Amended by Regulation no. 1839 of 18 December 2009
Poland	5 years	Sponsor and investigator are required to keep records of a clinical trial for a period of five years from the beginning of the calendar year following the year of the completion of	Section 2a Clinical trials of medicinal products, Art. 37ra., 1., Page 60	USTAWA, Prawo farmaceutyczne (The Pharmaceutical Act, 6 September 2001) Kancelaria Sejmu, 2013

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Country	Period of Storage	Requirement	Section	Document
		the clinical trial.		
Romania	Adheres to the European Union Directive Regulations & Guidance.			
Russia	2 years	Documents must be kept for at least two years after the approval of the last application for registration of the drug in Russia and as long as none of the applications will not be pending and new applications will be planned, or at least two years after official end of the clinical development of the investigational product.	4.9.5	НАЦИОНАЛЬНЫЙ СТАНДАРТ РОССИЙСКОЙ ФЕДЕРАЦИИ. НАДЛЕЖАЩАЯ КЛИНИЧЕСКАЯ ПРАКТИКА (National Standard of the Russian Federation, Good Clinical Practice), Federal Agency, 2006
Slovakia	Adheres to the European Union Directive Regulations & Guidance.			

ISCT Recommendations

Country	Period of Storage	Requirement	Section	Document
South Africa	15 years	<p>6.6 Adequate steps must be taken to ensure that the hospital case records of all participants in clinical research are retained for 15 years or until, at least, two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product, which is no longer than the time to destruction interval in some hospitals and institutions.</p> <p>6.7 The period and conditions under which the documents should be saved is no different than those imposed on the principal investigator; i.e. 15 years after termination of the study and preferably for the commercial lifetime of the product.</p>	<p>6.6 Archiving by the Principal Investigator, paragraph 3; Page 56 6.7 Archiving by the Sponsor, paragraph 3; Page 56</p>	<p>Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Department of Health, 2006</p>
Spain	Adheres to the European Union Directive Regulations & Guidance.			

ISCT Recommendations

Country	Period of Storage	Requirement	Section	Document
Sweden	2 years	Essential documents should be retained until at least 2 years after the last approval of a marketing application in the EU and until there are no pending or contemplated marketing applications in the EU or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or by agreement with the sponsor.	8. Duration for the Retention of Essential Documents, 8.1.2 Investigator / Institution Responsibilities	Detailed Guidelines on the Trial Master File and Archiving, European Commission, 2002
Switzerland	10 years	<p>1 The sponsor must archive all the data relating to the clinical trial until the expiry date of the last batch delivered of the preparation tested or the last medical device manufactured, but at least for ten years as of the date upon which the clinical trial is completed or halted.</p> <p>2 The investigator in charge must archive all the documents necessary for the identification and medical monitoring of the trial subjects as well as all other original data for ten years as the date upon which the clinical trial is completed or halted.</p>	Section 6: Mandatory information, report and security measures, Mandatory archiving, Article 25	Ordinance on clinical trials of therapeutic products 812.214.2, The Swiss Federal Council, the Federal Law on Therapeutic Products, 17 October 2001

ISCT Recommendations

Country	Period of Storage	Requirement	Section	Document
Turkey	5 years	All records related to the clinical trial will be regularly kept by sponsor and investigator, and maintained for not less than five years after the study is completed at all centers. In the case of implantable devices, the record retention period is not less than fifteen years. In the case of clinical trials involving cells or tissues, the records must be retained for not less than thirty years.	Chapter Eight Miscellaneous and Final Provisions, Clinical trial records and confidentiality, Article 28 (1)	Regulation on Clinical Trials By the Ministry of Health, First Clinical Research LLC, 2013
UK	5 years	The sponsor and the chief investigator shall ensure that the documents contained, or which has been contained, in the trial master file are retained for at least 5 years after the conclusion of the trial and that during that period are – (a) readily available to the licensing authority on request; and (b) complete and legible.	No. 1928, Regulation 18, 31A. Trial master file and archiving Regulation 1/2007 (7)	The Medicines for Human Use (Clinical Trials) Amendment Regulations, 2006