Title	Ongoing REB Review Activities
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N2/CAREB SOP CODE	SOP-404.002
Effective Date	~~2017-02-24~~2020-03-20

~~1. SITE APPROVALS~~

Status	Name and Title	Date
~~Authored~~Author of Harmonized Template	~~CAE, Manager~~SOPs, Institutional REBs	~~2017-02-20~~2019-04-01
Approved	~~Director, MUHC Centre for Applied Ethics~~MUHC REB Full Board Meeting	~~2017~~2020-02-~~20~~13
Acknowledge ~~of~~ receipt	MUHC Board of Directors	2020-03-20

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~~2.~~1. PURPOSE

This SOP describes the procedures for the ongoing review activities that occur after the initial Research Ethics Board (REB) approval of a research project and prior to the next formally scheduled continuing annual review of the research project.

~~3.~~2. SCOPE

This SOP pertains to REBs that review human participant research in compliance with applicable regulations and guidelines.

~~4.~~3. RESPONSIBILITIES

All REB members, ~~CAE Staff~~designated REB office personnel and Researchers are responsible for ensuring that the requirements of this SOP are met.

The Researcher is responsible for reporting to the REB any new information generated throughout the course of the research that might affect the rights, safety and well-being of research participants, including reportable events that meet the reporting criteria as per this SOP.

The Researcher is responsible for reporting to the REB any information about the conduct of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance.

When action is taken by the REB to ensure the protection of the rights, safety, and well-being of participants (e.g., for an unanticipated problem involving risks to participants or others) the REB is responsible for ~~reporting~~communicating the decision to the Researcher and ~~the~~, at the discretion of the board, relevant Organizational Official(s~~) and~~). The REB has the authority to notify the sponsor and/or the appropriate regulatory authorities of any ~~events~~event or exceptional circumstances that meet ~~the~~ reporting criteria. The REB may delegate regulatory authority reporting (as applicable) to the organization.

The REB Chair or designee is responsible for reviewing all reportable events submitted to the REB as well as any proposed ~~amendments~~amendment to the research, and for determining the type of review (i.e., delegated or Full Board) or action required. The REB must find that the criteria for approval are met before providing approval.

The REB members are responsible for reviewing any new information, reportable ~~events~~event or proposed ~~amendments~~amendment that are assigned to them or that are assigned to a Full Board meeting, and for recommending the appropriate course of action.

~~5.~~4. DEFINITIONS

See glossary of terms.

~~6.~~5. PROCEDURES

In addition to the formally scheduled continuing annual review, the REB must receive and review any new information generated throughout the course of the research that might affect the rights, safety and well-being of research participants and/or for which a preventative or corrective action is possible.

Such information may include: amendments, reportable events, relevant reports, or any other new information that may ~~adversely~~ affect the safety and well-being of the research participants or the conduct of the research.

Modifications to the approved research may not be initiated without prior REB review and approval except where necessary to eliminate apparent immediate hazards to human participants. If changes are made to eliminate immediate hazards, the Researcher must notify the REB immediately.

Multi-centered Research in Québec

- The REB will apply this SOP to studies for which it acts as the Evaluating REB for multi-centered research within the Québec health care network.
- In a multi-center study conducted by a different researcher at participating institutions with the same sponsor, each investigator is responsible for submissions of reportable events to the evaluating REB. The local researcher must submit in accordance with this SOP.
- Should researchers consider that the reportable event requires institutional involvement to ensure local participant safety and well-being, they may choose to inform the "personne formellement mandatée".
- An investigator within the Québec health care network who submits an amendment for approval to the Evaluating REB, must forward the approved amended documents as well as a copy of the original document with approved changes highlighted to the mandated person in each public institution where the research is taking place.
- For multi-centre trials within the Québec health care network, all participating sites within the Québec health care network covered by the evaluating REB's approval will be considered local.
- Requests to convert a study into a multicentre project or to add at least one site to a multi-centre study must be done via the Nagano platform, using the appropriate Form.

~~6.1.~~5.1. Amendments to ~~the~~ Approved Research

~~6.1.1.~~5.1.1. The Researcher is responsible for submitting~~, via NAGANO Form F1,~~ to the REB any ~~changes~~change to ~~the~~an approved ~~research in the form of an amendment~~project. Changes to the approved ~~research~~study may include~~ modifications including (for example),~~ for instance, modifications to the research protocol, to the consent form, to the Investigator Brochure (IB) or product monograph (PM), ~~changes in~~to the participant materials (e.g., wallet cards, diary cards, recruitment materials), ~~a change in~~to who the Researcher is, etc.;

~~6.1.2.~~5.1.2. When the amendment is the result of a sponsor safety notice or action letter, this document must be appended to the amendment request~~.~~;

~~6.1.3.~~5.1.3. When the amendment includes a change to the consent form, the Researcher must indicate his/her recommendation ~~for the provision of~~as to whether the new information should be provided to current and/or past research participants;[1]

[1] Civil Code of Québec, s. 10 par. 2, 20 and 21.

6.1.4.5.1.4. The REB Chair or designee pre-reviews the amendment to determine the appropriate level of REB review required (i.e., Full Board or delegated review) in accordance with ~~MUHC~~ REB SOP Delegated Review. If the proposed change represents more than minimal risk, it must be reviewed by the REB at a Full Board meeting. Amendments that may be classified as more than minimal risk may include:

- Addition of genetic testing, new genetic tests, or tissue banking where genetic testing may or will be performed,
- Addition of an open label extension phase following a randomized trial,
- Emergency amendments that arise because of participant safety ~~and~~, which may include, but are not limited to:

~~o~~ A change in ~~drug dosing/duration of exposure,~~

- ~~A change in~~ the recruitment ~~that may affect confidentiality or the perception of coercion,~~ ~~o~~ A change in experimental procedure or research population~~;~~.

6.1.5.5.1.5. For amendments requiring Full Board review, the ~~responsible CAE Personnel~~designated REB office personnel assigns the amendment to the next available Full Board meeting. For amendments that meet the criteria for delegated review, the ~~responsible CAE Personnel~~designated REB office personnel will ~~forward~~assign the amendment to the designated reviewer(s);

6.1.6.5.1.6. When an amendment involves ~~a revised~~revisions to the consent form, the REB will consider the recommendations of the Researcher in determining if, how and when the new information should be provided to the research participants and whether re-consent is required;

6.1.7.5.1.7. ~~The amended research~~Amendments may not be implemented prior to the REB review and approval, except when necessary to eliminate immediate hazards to participants. A change to the research that was initiated without prior REB review to eliminate an apparent immediate hazard to a research participant must be reported to the REB immediately;

6.1.8.5.1.8. Amendments considered to be administrative in nature (for example, change of address or change in administrative research staff) that have no impact on participants or their well-being~~,~~ may be submitted at the time of formally scheduled continuing annual ~~renewal~~review of the project ~~using Nagano Form F1~~;

6.1.9.5.1.9. The REB must find that the criteria for approval are still met in order to approve the amendment. Some documents submitted in an amendment may be acknowledged.

~~6.2.~~5.2. Reportable Events

The Researcher is responsible for submitting reportable events or findings that meet the REB's reporting criteria in accordance with this SOP and within the time frame specified in section 5.4. All reports submitted to the REB must have all research participant identifiers removed (i.e., participant research number only); The Researcher must determine if an event meets the REB reporting criteria:

As a general rule, any new information that would require a modification to the Investigator's Brochure, the research or the consent form, or would prompt ~~other~~an action by the REB to ensure protection of research participants~~,~~; any unanticipated ~~problems, events~~problem, event or ~~reports~~report that could significantly

impact the overall conduct of the research or alter the participants' willingness to participate or the REB's approval or favorable opinion to continue the research, must be reported to the REB.

The Researcher must report the following to the REB, via NAGANO, within the ~~–~~time ~~–~~frame specified by the REB~~ ~~(5.4~~):~~)~~.

~~6.2.1.~~5.2.1. Local Serious Adverse Events (SAE~~)~~):

- The Researcher must report to the REB~~,~~ any local ~~incident, experience, or outcome (including an~~serious adverse event~~)~~ that, in the opinion of the Researcher, meets all of the ~~definition of an unanticipated problem~~following criteria:
  a) Unexpected ~~and;~~;
  b) Related or possibly related to participation in the research; and~~;~~
  c) Suggests that the research places research participants or others at a greater risk of harm than previously identified at time of review and approval.
- The report submitted to the REB, via Nagano, must include all of the following information:
  a) The description of the adverse event;
  b) Previous safety reports concerning similar events, if available;
  c) An analysis of the significance of the current adverse event; and
  d) If applicable, the proposed modifications to the conduct of the research project and/or to the informed consent form and/or a list of corrective actions to be taken in response to the event;
  e) A copy of the sponsor's report, if available.
- Any applicable ~~forms~~form completed/required by the sponsor ~~(ex.~~, if any, (e.g., SAE form), must be ~~appended~~uploaded to ~~the~~ Nagano ~~Form F3a (Reportable Local SAE);~~;
- Once a local SAE is reported to the REB, subsequent important follow-up reports related to the SAE should be submitted ~~when~~as soon as available~~, as update(s).~~. The ~~sponsor's~~ follow-up ~~reporting form(s)~~reports from the sponsor must be ~~appended to~~transmitted when updating the ~~updated~~ reportable event. All initial and subsequent follow-up reports will be retained with the ~~reportable event~~initial declaration.

~~6.2.2.~~5.2.2. Non-Local (External) Serious Adverse Events (SAE)

- The Researcher must report to the REB, any non-local ~~incident, experience, or outcome (including an~~serious adverse event~~)~~ that, in the opinion of the Researcher, meets all of the ~~definition of an unanticipated problem~~following criteria:
  a. Unexpected ~~and;~~;
  b. Related or possibly related to participation in the research ~~and;~~;
  c. Suggests that the research places research participants or others at a greater risk of harm than previously identified at time of review and approval;

AND

~~d)~~f) Requires a change to the research and/or informed consent form and/or requires immediate notification to participants for safety reasons.

~~e)~~ The report submitted to the REB, via Nagano~~ Form F3a (Local Reportable SAE),~~ must include all of the ~~following~~ information~~:~~

~~a. The description of the unanticipated problem,~~

~~b. Previous safety reports concerning similar events, if available,~~

~~c. An analysis of the significance of the current unanticipated problem, and~~

~~d. The proposed research changes, informed consent form changes or other corrective actions to be taken by the sponsor~~ listed in ~~response to the event(s),~~ section 5.2.1.

~~f) A copy of the sponsor's report, if available.~~

~~6.2.3.~~5.2.3. Deviations to Previously Approved Research

The Researcher must report to the REB, in Nagano~~ Form F3b (Other Reportable events: Deviations, Privacy Breaches, Complaints),~~ any local ~~deviations~~deviation that ~~meet~~meets the following reporting criteria:

- Deviations that, in the opinion of the Researcher: jeopardize the safety of research participants, the research efficacy, data integrity, or that could otherwise ~~could~~ impact participant rights, safety or well-being;
- Any sponsor-approved ~~waivers~~waiver to the participant eligibility criteria~~,~~;
- Any change in the approved process for obtaining consent (e.g., improper translation, current ~~ICF~~consent form not implemented);
- Any ~~deviations~~deviation that leads to an SAE.

~~6.2.4.~~5.2.4. Privacy Breaches

- The Researcher must report to the REB, ~~using~~in Nagano~~ Form F3b (Other Reportable events: Deviations, Privacy Breaches, Complaints),~~ any unauthorized collection, use, or disclosure of personal information including, but not limited to:

- The collection, use and disclosure of personal information that is not in compliance with the ~~jurisdictional~~applicable legislation or ~~its~~ regulation,
- Circumstances where personal information is stolen, lost or subject to unauthorized use or disclosure or where records of personal information are subjected to unauthorized copying, modifications or disposal,
- ~~In the Researcher context, any~~Any unauthorized collection, ~~-~~use or ~~-~~disclosure of personal information done in the context of the research project but that was not ~~authorized under the research and~~ approved ~~in the plan that was submitted to~~by the REB~~,~~.
- The breach must ~~-~~be reported to the REB and, ~~if~~ as applicable, to the appropriate Organizational Official(s) as soon as the Researcher becomes aware of the breach.

~~6.2.5.~~5.2.5. Research Participant Complaint

The Researcher must report to the REB, ~~using~~in Nagano~~ Form F3b (Other reportable events: deviation, privacy breaches, complaints, a complaint from~~, any concern raised by a participant~~) when the participant reports concerns~~ about their rights as a research participant or about ethical issues related to the research~~ as per SOP 406.001~~.

~~6.2.6.~~5.2.6. Other Reportable Events ~~or Findings~~and Information

- The Researcher is responsible for reporting to the REB, using the appropriate Nagano ~~form for Amendments F1, Other Correspondence F2, Reportable events F3, Change of Status F6, etc., other events or findings, including~~forms, circumstances such as:

- Any ~~changes~~change to the risks or potential benefits of the research, ~~such as~~including:
  - An interim analysis ~~indicates~~indicating that participants have a ~~lower~~ rate of response to treatment different than ~~initially~~ expected,
  - Safety monitoring ~~indicates~~indicating that a particular side effect is more severe~~,~~ or more frequent than ~~initially~~ expected,
  - Information ~~is~~ published from another research project that shows that an arm of the research is of no therapeutic value;
  - A change in Health Canada or FDA safety labeling, approval status or withdrawal from ~~marketing~~market of a drug, device, health product, genetic therapy or biologic used in ~~research~~the project;
  - Any unanticipated ~~problems~~problem or other ~~events~~event that could significantly impact the conduct of the research at the site (e.g., concerns of non-compliance, institutional feasibility issues etc.);
  - ~~Any relevant findings~~Findings of an inspection or audit relevant to the safety and well-being of the participants: The Researcher must report to the REB a summary of any relevant audit or inspection ~~findings~~finding relevant to the safety and well-being of the participants following a ~~–~~Health Canada inspection, an FDA or other regulatory audit, an internal ~~QA~~Quality Assurance audit, or other audits at the site.

5.3. Other reports

- The Researcher is responsible for submitting to the REB, using Nagano~~ form F2~~, reports related to the research in accordance with 5.4:

- ~~Reports~~If the sponsor requires the submission to the REB of reports that are generated in accordance with the research protocol or that are routine or random **and that do not require action** to protect the safety and well-being of research participants, these reports may be submitted~~, if required by the sponsor,~~ at the time of formally scheduled continuing annual ~~renewal~~review. The REB will acknowledge receipt of ~~these~~such reports.

~~6.3.~~5.4. Time frames for reporting events to the REB

The REB must be notified of reportable events as described in this SOP in accordance with the following timelines:

REB notification of…	Time delay (calendar days)	Follow up required
5.4.1 Amendments		
a) ~~a.~~ Undertaken immediately to protect participants	Immediately	REB review and approval of amendments
b) ~~b.~~ All other amendments	Report prior to introducing any change	REB review and approval are required prior to ~~initiation~~implementation of the amendment~~.~~
5.4.2 All ~~Reportable~~reportable events as described herein		
a) ~~a.~~ Reportable events in context of death and/or life-threatening reactions~~:~~	Within 7 days of researcher becoming aware of the event~~.~~	A detailed report containing an analysis of the event, its consequences and corrective measures taken must be submitted within 8 days of the first report
b) ~~b.~~ All other reportable events	Within 15 days of researcher becoming aware of the event	
~~**5.3 Reports**~~		
~~Scheduled, routine or random reports without identified impact on participant safety or well-being or required changes~~	~~Submit at time of annual renewal~~	~~REB acknowledgement letter will be sent.~~
c) Any new information that may adversely affect the safety of the research participants or the conduct of the research	Within 15 days of researcher becoming aware of this info	

5.4.3 Other reports		
Scheduled, routine or random reports without identified impact on participant safety or well-being or required changes	Submit at the time of continuing review if required by the Sponsor.	REB acknowledgement letter will be sent.

~~6.4.~~5.5. Review of Reportable Events by the REB

~~6.4.1.~~5.5.1. The ~~responsible CAE Personnel~~designated REB office personnel will screen the submission for completeness and to ensure that the ~~MUHC REB~~ reportable event form ~~is used~~was attached, if applicable;

~~6.4.2.~~5.5.2. ~~The CAE Personnel~~The designated REB office personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information;

~~6.4.3.~~5.5.3. The ~~CAE Personnel~~designated REB office personnel will ~~forward~~assign the submission to ~~the designated~~ REB reviewer(s);

~~6.4.4.~~5.5.4. The assigned REB reviewer(s) will conduct a review of the report and determine if any action or follow-up is required. The assigned reviewer(s) may request further information from the Researcher;

~~6.4.5.~~5.5.5. When reviewing a reportable event, the REB ~~should~~must:

- Assess the appropriateness of any ~~proposed~~ corrective or preventative ~~measures~~ measure proposed by the sponsor and/or Researcher,
- Consider any additional appropriate ~~measures~~measure that may or may not have been identified or proposed by the sponsor and/or Researcher,
- Consider whether the ~~affected research~~project still satisfies the requirements for REB approval~~;~~, in particular whether risks to research participants are still minimized and reasonable in relation to the anticipated benefits~~,~~(if any~~,~~) to the research participants, and ~~the importance of~~whether the knowledge that may reasonably be expected to ~~result~~accrue from the project is sufficiently important,
- Consider whether some or all of the research participants should be notified of the events (i.e., if it may affect ~~the participant's~~participants' willingness to continue ~~participation~~participating in the research), and
- Consider whether suspension or termination of the ethics approval of the research is warranted;

~~6.4.6.~~5.5.6. Privacy breaches are reviewed by the REB Chair or designee, and any ~~recommendations~~recommendation including remedial action ~~are~~is determined in consultation with the organization's ~~privacy office~~responsible authority;

~~6.4.7.~~5.5.7. If the event does not raise concerns and does not appear to involve risks to research participants or others, the REB Chair or designee acknowledges the report, and no further action is required;

5.5.8. If the REB Chair or designee determines that ~~the event meets the criteria for an unanticipated problem, and if~~ immediate action is required to protect the safety and well-being of research participants, he/she may ~~suspend~~:

- Put recruitment of new participants on hold, including participants in the screening process,
- Suspend ethics approval of the research (put study on Hold~~) pending review by the Full Board, providing the justification for such~~),
- Take any other action ~~is documented~~deemed necessary;

~~6.4.8.~~5.5.9. If the event raises concerns or involves risk to research participants such that REB action ~~may be~~is required, the item ~~is~~must subsequently be reviewed ~~by~~at a Full Board meeting;

~~6.4.9.~~5.5.10. For reportable events reviewed at ~~by~~ a Full Board meeting, the REB determines whether further action is required. Possible actions that could be taken by the REB include, but are not limited to:

- Placing a hold on the research pending receipt of further information from the Researcher,
- Requesting modifications to the research,
- Requesting modifications to the consent form,
- ~~Providing~~Requesting additional information be provided to past participants,
- ~~Notifying~~Requesting current participants be notified when such information might affect the participants willingness to continue to take part in the research, and requiring that current participants re-consent for ongoing participation,
- Altering the frequency of continuing review,
- Observing the research or the consent process,
- Requiring additional training of the Researcher and research staff,
- ~~Termination~~Terminating or ~~suspension of~~suspending the research,
- If the REB determines that the event does not raise concerns about risks to research participants, the REB may decide that no further action needs to be taken;

~~When action is taken to ensure the protection of the rights, safety, and well-being of participants (e.g., for an unanticipated problem involving risks to participants or others) the REB chair or designee is responsible for reporting to the Researcher and MUHC/RI Official(s) and has the authority to notify the sponsor and the appropriate regulatory authorities (as applicable). The REB may delegate regulatory authority reporting (as applicable) to the organization~~

~~5.1. AMENDMENTS AND REPORTABLE EVENTS IN THE CONTEXT OF MULTI-CENTERED RESEARCH:~~

~~The MUHC REB will apply this SOP to studies for which it acts as the Evaluating REB for multi-centered research within the Québec public health care system.~~

~~In a multi-center study conducted by a different researcher at participating institutions with the same sponsor, each investigator is responsible for submissions of reportable events in their institution and to the Evaluating REB. The local MUHC researcher must submit in accordance with this SOP.~~

~~A Quebec investigator who submits an amendment for approval to the Evaluating REB, must forward the approved amended documents as well as a copy of the original document with approved changes highlighted to the mandated person in each public institution where the research is taking place.~~

~~For multi-centre trials in Québec for which the MUHC is the evaluating REB, all participating site within the Québec public health care system covered by the MUHC REB approval will be considered local.~~

~~Adding a site that transforms your project into a multicentre project, or that adds a site to a multi-centre study, must use Nagano Form F1MP.~~

5.5.11. Amendments to consent:

5.5.11.1. Information relevant to consent that becomes available during a research project or after it has been completed/terminated:

- The REB reviews and approves the information that must be brought to the attention of participants of an ongoing project, the process to disclose to participants potential long-term health effects during or after research participation, and changes to the consent form that require that new information be transmitted to participants;[2]

5.5.11.2. The Researcher informs participants of any new information that may affect their willingness to continue to participate in research (e.g., significant change in the project or its associated risks),[3] as well as of any new information regarding the potential impacts of the research project on their long-term health, even if their participation has already ended;

5.5.11.3. The REB determines:

a) The nature of the new information to be transmitted to participants whose participation is ongoing, and the documentation that is required,

[2] *Modèle*, s. 10.4.
[3] *TCPS2*, s. 3.3.

b) Whether an update to the consent form is required,

c) The process that must be put in place to allow participants to reconsent to participating in the ongoing research project;[4]

5.5.11.4. If applicable, the REB may allow consent to be obtained orally via a telephone conversation during which the updated information would be provided.[5] The participant's consent to continue participating will be documented;

5.5.11.5. The Researcher must inform former research participants of any new information that may be relevant to their long-term health by contacting them by phone, mail, or in person, if applicable.

6. REFERENCES

See footnotes and the following references:

- Canadian Association of Research Ethics Boards. History of the Development of the Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada July 2010.
- ICH E2A, II.A.1
- ICH E6: Good Clinical Practice (GCP), 5.17
  - ~~MUHC, RI SOP-007~~
  - ~~MUHC, RI SOP-012~~
- N2 CAREB REB SOPs September 15, 2014, https~~://www.careb-accer.org/n2careb-accer-reb-~~://www.careb-accer.org/n2careb-accer-reb- sops
- Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) – Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events~~, http://www.hhs.gov/ohrp/policy/advevntguid.pdf~~, http://www.hhs.gov/ohrp/policy/advevntguid.pdf
- Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2014 (TCPS2)
- USA Food and Drug Administration Code of Federal Regulations Title 21 Part 56.108 (b)
- US Department of Health and Human Services. Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting, January, 2009. ~~http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/~~

[4] Be reminded that consent to participate in research may be withdrawn at any time, even verbally. See: Civil Code of Québec, s. 24 par. 3.
[5] Civil Code of Québec, s. 24 par. 2.

~~ucm079753.pdf~~http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ ucm079753.pdf

- ~~See References~~

~~1. REVISION HISTORY~~

7. REVISION HISTORY

SOP Code	Effective Date	Summary of Changes
~~SOP-~~REB-~~404~~SOP 405A.001	~~2016-02-22~~N.A.	~~First issue~~Original Version
~~MUHC-~~REB-SOP-~~405.002~~ 405A.001-1	~~2017-02-24~~2020-03-20	~~MUHC SOP Code and minor page layout changes~~5.2.5: deletion of the reference to MON406
~~MUHC-REB-SOP-405.002_1~~	~~2017-07-07~~	~~5.1.4. Change to reference to MUHC-REB SOP-402.001.~~ ~~5.2.2. Change of Form reference (From F1 to F3a)~~ ~~5.2.5. Change of Form reference (From F8 to F3b)~~ ~~5.4. Time delay changed from 14 to 15 days.~~ ~~6. Corrected references: harmonized with RI- SOPs.~~

8. APPENDICES