



## Guidance on Resubmissions and Amendments of ISAC Research Protocols

**This guidance document has been produced to help applicants resubmit an ISAC Protocol Application, or submit proposed amendments to approved ISAC Research Protocols. Resubmissions and Amendments not completed in accordance with the guidance will be returned as invalid.**

### Protocol Resubmissions

The ISAC may request resubmission of a Protocol Application where further information is required before approval can be granted. Feedback will be provided by the ISAC on the points to be addressed in any resubmission.

The format of resubmissions should be as follows:

- The ISAC Feedback Form, with applicant's responses to each of the questions or issues raised by the reviewers;
- An updated ISAC Protocol Application Form, with all changes from the originally submitted protocol highlighted in yellow using the highlight feature.

Please note that track changes and strikethrough text are not permitted, and applications resubmitted with track changes or strikethrough will be returned as invalid.

Resubmissions of ISAC Protocol Applications should be received by the ISAC Secretariat within 6 months of the date of ISAC feedback. Protocols that do not receive a resubmission within 6 months of the feedback date will be held to be withdrawn, and applicants will be required to submit a new ISAC Protocol Application. The ISAC Secretariat should be contacted if there are circumstances which may result in the resubmission exceeding the 6-month deadline.

In cases where the applicant(s) do not intend to resubmit a Protocol Application to the ISAC, the Secretariat should be contacted, and the protocol withdrawn. Please email [isac@cprd.com](mailto:isac@cprd.com) for advice.

### Protocol Amendments

During the course of some studies, it may become necessary to deviate from an ISAC approved protocol. Any small deviations from an approved protocol should be reported to the ISAC Secretariat as a minor amendment, and significant deviations from an approved protocol will require ISAC approval as a major amendment.

In cases of uncertainty, the applicant should contact the ISAC Secretariat at [isac@cprd.com](mailto:isac@cprd.com) for advice, quoting the ISAC Protocol Number and providing a brief explanation of the nature of the amendment(s) and underlying reason(s).

### Major Amendments

Protocol deviations that substantially change the study design or analysis plan of the proposed research warrant submission of a major amendment request to the ISAC for approval. An amendment is considered to be major if it involves the following (although this is not an exhaustive list):

- A change to the primary hypothesis being tested in the research;
- A change to the study design;
- Additional outcomes or exposures relating to new hypotheses (please note that extensive changes in this respect may require submission of a new ISAC Protocol Application);
- Non-trivial changes to the analysis strategy;
- Not performing a primary outcome analysis;



- Omissions from the analysis plan which may impact on important validity issues such as confounding;
- Change of Chief Investigator;
- Use of additional linkages to other databases;
- Any new proposal involving contact with health professionals or patient or change regarding such matters.

To submit a major amendment request, please provide the following documents to the ISAC Secretariat ([isac@cprd.com](mailto:isac@cprd.com)):

1. A covering letter providing justification for the request, addressed to the ISAC, and signed by the Chief Investigator;
2. A completed and updated ISAC Protocol Application form:
  - a. All changes to Part 1 of the form should be highlighted in yellow using the highlight feature;
  - b. There should be no changes to Part 2 of the application. Instead, applicants should create a new section with the heading 'Amendment - DATE' at the end of Part 2. Please include all proposed amendments to Part 2 under this heading, using the same sub-headings as in Part 2 of the application.

Major amendment requests that do not follow this format will be returned as invalid.

### Minor Amendments

Examples of protocol deviations which generally constitute a minor amendment include the following:

- Change of personnel other than the Chief Investigator;
- A change to the definition of the study population, providing the change is mentioned and justified in the paper/output;
- Extension of the time period in relation to defining the study population;
- Changes to the definitions of outcomes or exposures of interest, providing the change is mentioned and justified in the paper/output;
- Additional outcomes or exposures which are related to the main focus of the approved protocol (e.g. death from pancreatic cancer in an approved protocol of pancreatic cancer);
- Not using linked data which are part of the approved protocol (applicants should justify how this will not significantly impact on the study. Where not using linked data is likely to have a significant impact, this will require a major amendment);
- Limited additional analysis suggested by unexpected findings, provided these are clearly presented as post-hoc;
- Additional methods to further control for confounding or sensitivity analysis provided these are to be reported as secondary to the main findings;
- Validation and data quality work provided additional information from GPs is not required.

To submit a minor amendment request, please provide the following documents to the ISAC Secretariat ([isac@cprd.com](mailto:isac@cprd.com)):

1. A covering letter detailing the proposed minor amendment(s), providing justification, addressed to the ISAC, and signed by the Chief Investigator.

**Please note that applicants should receive approval for both major and minor amendments. Amendments that do not receive approval are not valid, and any studies published with unapproved deviations will be in breach of contract.**