Guidelines on Reviewing and Reporting Unanticipated Problems Involving Risks to Subject or Others and Adverse Events

Ministry of Public Health
Department of Research

Scope: This document provides guidance on regulations for the protection of human research subjects related to the review and reporting of (a) unanticipated problems involving risks to subjects or others; and (b) adverse events. The guidance is intended to help ensure that the review and reporting of unanticipated problems and adverse events occur in a timely, meaningful way so that human subjects can be better protected from avoidable harms while reducing unnecessary burden.

The Qatar Health Research Ethics Committee has unanimously approved this document. A law to legally enforce this document is in process.

Background:

Guidelines, Regulations and Policies for Research Involving Human Subjects issued by Qatar Ministry of Public Health contain specific requirements relevant to the review and reporting of unanticipated problems and adverse events. The requirements specify that:

(1) Institutions engaged in human subjects research must have procedures for ensuring prompt reporting and must report any unanticipated problem involving risks to subjects to the IRB, institutional officials, funding entity and Department of Research, Qatar Ministry of Public Health.

(2) The IRB must determine, among other things, that:
(a) Risks to subjects are minimized.
(b) Risks to subjects are reasonable in relation to anticipated benefits.
(c) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(3) An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

(4) An IRB must have authority to suspend or terminate **approval** of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

I. Unanticipated problems

The Qatar Ministry of Public Health considers **unanticipated problems**, in general, to include any incident, experience, or outcome that **meets all of the following criteria:**

(1) unexpected in terms of nature, severity, or frequency as given in the IRB approved research protocol and informed consent document;

(2) there is a reasonable possibility that it is related or possibly related to participation in the research; and

(3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Qatar Ministry of Public Health recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. However, an incident, experience, or outcome that meets the three criteria above whether they involve social or economic harm or physical or psychological harm generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

II. *Adverse events*:

In this guidance document, the term ***adverse event*** is used very broadly and includes any event meeting the following definition:

Any unfavorable medical occurrence including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

III. Determination of which *adverse events* are *unanticipated problems*:

It is anticipated that most IRB members, investigators, and institutional officials understand the scope and meaning of the term *adverse event* in the research context, but lack a clear understanding as to what, when, and to whom adverse events need to be reported as unanticipated problems. If adverse events occurring in human subjects are not unanticipated problems, those need not be reported. On the other hand, if adverse events are unanticipated problems; or unanticipated problems are not adverse events, all need to be reported. The key question regarding a particular adverse event is whether it meets the three criteria described in above and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes,* then the adverse event is an unanticipated problem and **must be reported** to appropriate entities. The next threesub-sections discuss the assessment of these three questions.

A. Assessing whether an adverse event is unexpected

In this guidance document, *unexpected adverse event* is defined as any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

(1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the IRB approved research protocol; or

(2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

B. Assessing whether an adverse event is related or possibly related to participation in research

Adverse events may be caused by:

(1) the procedures involved in the research;
(2) an underlying disease, disorder, or condition of the subject; and/or
(3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

Determinations about the relatedness of adverse events to participation in research commonly result in probability statements that fall along a continuum between definitely *related* to the research and definitely *unrelated* to participation in the research. *Possibly related* to participation in the research is considered to be an important threshold for determining whether a particular adverse event represents an unanticipated problem. In this guidance document, *possibly related* is defined as follows: "There is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research".

Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported.

C. Assessing whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*. In this guidance document, *Serious adverse event* is defined as any adverse event that:

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;

(5) results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

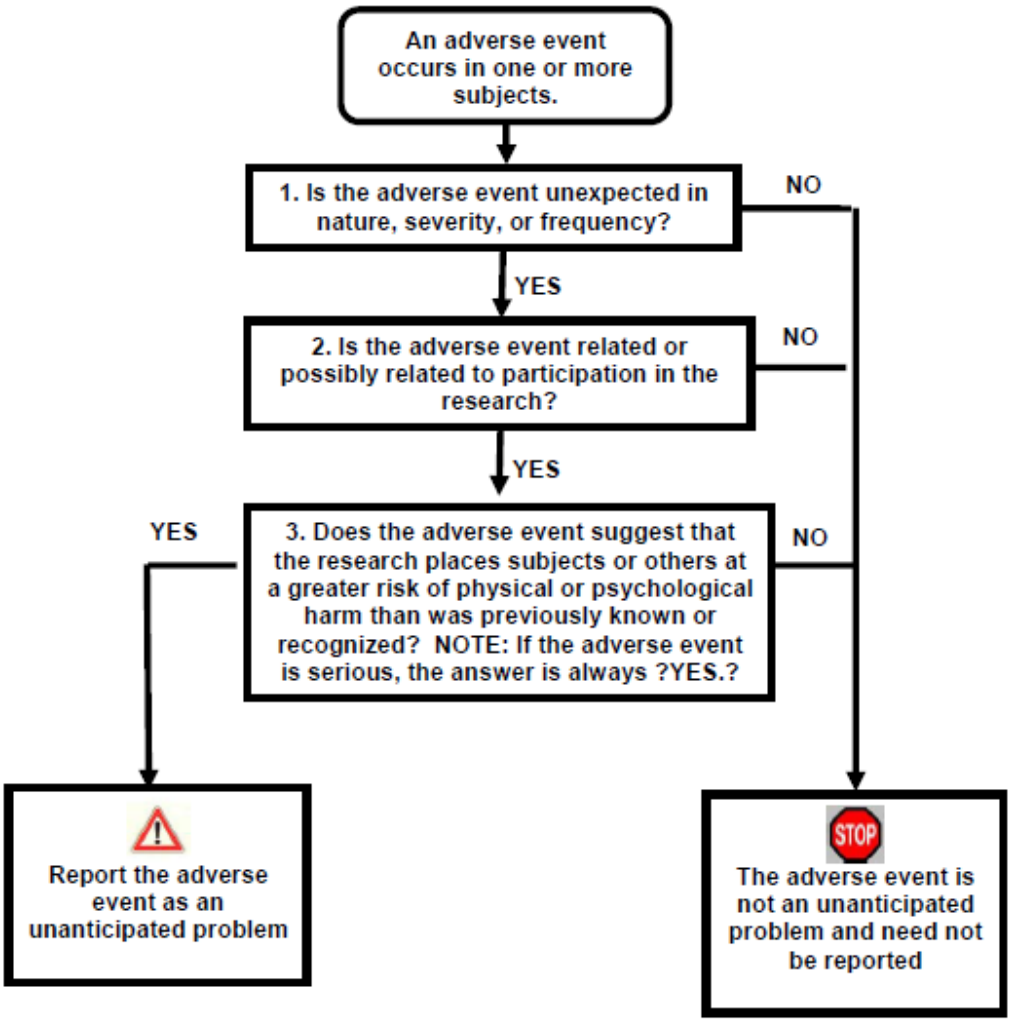
Adverse events that are unexpected, related or possibly related to participation in research, and *serious* are considered to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Furthermore, Department of Research at the Qatar Ministry of Public Health notes that IRBs have authority to suspend or terminate **approval** of research that, among other things, has been associated with unexpected serious harm to subjects. In order for IRBs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, related or possibly related to participation in the research, and serious.

However, other adverse events that is unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



IV. Other important considerations regarding the reviewing and reporting of unanticipated problems and adverse events:

A. Reporting of *internal* adverse events by *investigators*

Upon becoming aware of an adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the guidelines described above. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.

Regardless of whether the adverse event is determined to be an unanticipated problem, the investigator also must ensure that the adverse event is reported to a monitoring entity (e.g., a coordinating or statistical center or a DSMB/DMC) *if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy*.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.

B. Reporting of *external* adverse events by *investigators*

Department of Research at Qatar Ministry of Public Health notes that reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Therefore, individual adverse events occurring in subjects enrolled in multicenter studies should only be reported to investigators and IRBs at all institutions **when** a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB at each institution. Typically, such reports to the IRBs are submitted by investigators. Department of Research at Qatar Ministry of Public Health recommends that any distributed reports include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

(1) unexpected;

(2) related or possibly related to participation in the research; and

(3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems.

C. Reporting of *other unanticipated problems* (not related to adverse events) by *investigators*

Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described above. If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.

D. *Content of reports* of unanticipated problems

Department of Research at Qatar Ministry of Public Health recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health:

(1) appropriately identify information in connection wih the research protocol, such as the title, investigator's name, and the IRB project number;

(2) a detailed description of the adverse event, incident, experience, or outcome;

(3) an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and

(4) a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

E. IRB review and further reporting of unanticipated problems

Once reported, further review and reporting of any unanticipated problems must proceed in accordance with the institution's procedures for reporting unanticipated problems. Since there are no specific requirements for how such unanticipated problems are reviewed, IRBs are free to implement a wide range of procedures for reviewing unanticipated problems, including review by the IRB chairperson or another IRB member, a subcommittee of the IRB, or the convened IRB, among others. When reviewing a report of an unanticipated problem, the IRB should consider whether the affected research protocol still satisfies the requirements set by the Ministry of Public

Health's Guidelines, Regulations and Policies for Research Involving Human Subjects. In particular, the IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result. The IRB has authority to require, as a condition of continued approval, submission of more detailed information by the investigator or DSMB/DMC about any adverse event or unanticipated problem occurring in a research protocol.

Any proposed changes to a research study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to subjects. Department of Research recommends that for multicenter research protocols, if the IRB proposes changes to the protocol or informed consent documents/process in addition to those proposed by the coordinating center or local investigator, the IRB should request in writing that the local investigator discuss the proposed modifications with the funding entity or coordinating center and submit a response or necessary modifications for review by the IRB.

Institutions must have written procedures for reporting unanticipated problems to appropriate institutional officials. Institutions may develop written procedures that specify different institutional officials as being appropriate for different types of unanticipated problems.

V. Time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the Department of Research and the funding body:

Written procedures are required for ensuring *prompt* reporting of unanticipated problems. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, Department of Research recommends the following guidelines in order to satisfy the requirement for *prompt* reporting:

(1) Unanticipated problems that are serious adverse events should be reported to within 1 week of the investigator becoming aware of the event.

(2) Any other unanticipated problem should be reported within 2 weeks of the investigator becoming aware of the problem.

(3) All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's reporting procedures), the funding body, and Department of Research at Qatar Ministry of Public Health, and within one month of the IRB's receipt of the report of the problem from the investigator.

Department of Research notes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

VI. Issues to be considered with respect to adverse events:

Before research is approved and the first subject enrolled, the investigator(s) should give appropriate consideration to the spectrum of adverse events that might occur in subjects. In particular, determinations should be made as to whether the IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may be caused by the procedures involved in the research. The investigator also should describe how the risks of the research will be minimized.

In addition, depending upon the risks of the research and the likelihood that the research could involve risks to subjects that are unforeseeable, the investigator should provide information that includes adequate provisions for monitoring the data collected to ensure the safety of subjects. Such provisions typically would include monitoring, among other things, adverse events and unanticipated problems that may occur in subjects enrolled in the research.

Department of Research notes that adequate monitoring provisions for research, if deemed appropriate by the IRB, might include one or more of the following elements, among others:

(1) The type of data or events that are to be captured under the monitoring provisions.

(2) The entity responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the funding entity, a coordinating or statistical center, and/or DSMB/DMC).

(3) The time frames for reporting adverse events and unanticipated problems to the monitoring entity.

(4) The frequency of assessments of data or events captured by the monitoring provisions.

(5) Definition of specific triggers or stopping rules that will dictate when some action is required.

(6) As appropriate, procedures for communicating to the IRB(s), the funding entity, the investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.

The monitoring provisions should be tailored to the expected risks of the research; the type of subject population being studied; and the nature, size, and complexity of the research protocol. For example, for a multicenter clinical trial involving a highlevel of risk to subjects, frequent monitoring by a DSMB/DMC may be appropriate, whereas for research involving no more than minimal risk to subjects, it may be appropriate to not include extensive monitoring provisions.

VII. Issues for the IRB should consider at the time of continuing review with respect to unanticipated problems and adverse events:

The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. At the time of continuing review, the IRB should ensure that the criteria for IRB approval continue to be satisfied. In particular, the IRB needs to determine whether any new information has emerged either from the research itself or from other sources that could alter the IRB's previous determinations, particularly with respect to risk to subjects. Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review.

It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

Department of Research recommends that, among other things, a summary of any unanticipated problems and available information regarding adverse events and any recent literature that may be relevant to the research be included in continuing review reports submitted to the IRB by investigators. Department of Research notes that the amount of details provided in such a summary will vary depending on the type of research being conducted. In many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

In multicenter clinical trials, local investigators may not be able to prepare a meaningful summary of adverse events because study-wide information regarding adverse events is not readily available to them. In such circumstances, when the clinical trial is subject to oversight by a monitoring entity (e.g., a coordinating or statistical center or a DSMB/DMC), Department of Research recommends that at the time of continuing review local investigators submit to their IRBs a current report from the monitoring entity. Further, it is recommended that such reports include the following:

(1) a statement indicating what information (e.g., study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;

(2) the date of the review; and

(3) the monitoring entity's assessment of the information reviewed.

VIII. What should written IRB procedures include with respect to reporting unanticipated problems?

Written IRB procedures should provide a step-by-step description with key operational details for complying with the reporting requirements described above. Important operational details for the required reporting procedures should include:

(1) The type of information that is to be included in reports of unanticipated problems.

(2) A description of which office(s) or individual(s) is responsible for promptly reporting unanticipated problems to the IRB, appropriate institutional officials, funding entity, and Department of Research.

(3) A description of the required time frame for accomplishing the reporting requirements for unanticipated problems.

(4) The range of the IRB's possible actions in response to reports of unanticipated problems. Department of Research notes that many institutions have written IRB procedures for reporting adverse events, but do not address specifically the reporting requirements for unanticipated problems. Such institutions should expand their written IRB procedures to include reporting requirements for unanticipated problems.