STANDARD OPERATING PROCEDURE

OBJECTIVE/SCOPE

To establish definitions and procedures for requesting or reporting protocol exceptions, deviations, and temporary variances to the National Marrow Donor Program (NMDP) Institutional Review Board (IRB).

MATERIALS

1. NMDP IRB Major Protocol Exception Request Form
2. Protocol Exceptions and Deviations Log
3. Temporary Variance Request Form

SAFETY

Not applicable

DEFINITIONS

1. **IRBManager:** Web-based system for IRB application submission, IRB application review, and management of IRB-related study records.
2. **IRB of record:** The IRB of record is the IRB responsible for conducting the IRB reviews of a study on behalf of a participating study site.
3. **Major protocol exception:** A protocol exception that may adversely affect one or both of the following:
    - the safety, rights, or welfare of the subject(s)
    - the scientific validity of the research
4. **Minor protocol exception:** A protocol exception that does not fit the criteria of a major protocol exception.
5. **Protocol amendment:** An intentional change to the previously IRB-approved protocol that is initiated by the investigator or sponsor and is implemented as a systematic change.

6. **Protocol deviation:** A departure from the IRB-approved protocol procedures that is unintentional and discovered after it occurs. The protocol deviation is not a result of willful or knowing misconduct by the investigator or research staff.

7. **Protocol exception:** A one-time, temporary departure from the IRB-approved protocol procedures that is identified before it occurs and intended for one specific study subject. Protocol exceptions do not have the intention of amending the protocol as a systematic change.

8. **Relying institution:** A participating study site that enters into a reliance agreement to rely on another IRB, rather than their own local IRB, for review and continuing oversight of the study at their institution.

9. **Temporary variance:** An intentional change to the previously IRB-approved protocol that is initiated by the sponsor/Study Chair and is implemented as a systematic change prior to an official protocol amendment.

RESPONSIBILITIES

1. **Relying institution's investigator**

    - Assess whether a protocol exception should be classified as major or minor.
    - Submit the *NMDP IRB Major Protocol Exception Request Form* for all major protocol exceptions to the NMDP IRB for approval prior to implementation
    - Maintain a copy of the NMDP IRB's approval of the major protocol exception
    - Assess minor protocol exceptions and protocol deviations that were not approved by the NMDP IRB prior to implementation for qualification as unanticipated problems or serious or continuing non-compliance, and follow procedures for reporting events if applicable.
    - Record all protocol exceptions and protocol deviations in a systematic manner to be reported to the NMDP IRB at the time of the study's next continuing review

2. **Study Sponsor or Study Chair**

    - Request approval by the NMDP IRB for a temporary variance prior to implementing the variance.

PROCEDURE

APPLICABILITY

1. This SOP applies to research sites that are relying on the NMDP IRB as their IRB of record for the study, and therefore fall under the jurisdiction of the NMDP IRB. Henceforth, these research sites shall be referred to as relying institutions. This includes Be The Match® donor centers that rely on the NMDP IRB for studies where the unrelated donor is

considered a human research subject. This also includes other research sites (e.g. transplant centers) that rely on the NMDP IRB for the study.

2. This SOP also applies to a network group/study sponsor/Study Chair who needs to request a study-wide protocol exception or temporary variance or report a protocol deviation to the NMDP IRB.

BACKGROUND

3. Departures from the IRB-approved protocol procedures occur for a variety of reasons, such as an investigator's intentional decision to deviate, a subject's lack of adherence to the protocol, or external/environmental factors. Some departures are intentional; some are not. Some departures are known about before they occur; some are discovered after they've occurred.

4. These departures from the IRB-approved protocol procedures are often referred to collectively in the clinical research setting as "protocol deviations." The purpose of this SOP is to differentiate between protocol exceptions, protocol deviations, and temporary variances and to establish reporting procedures for each.

MAJOR PROTOCOL EXCEPTIONS

5. It is the relying institution's investigator's responsibility to assess whether a protocol exception should be classified as major or minor. The NMDP IRB office is available to assist the investigator in this determination if needed.

6. One example of a major protocol exception would be the intent to enroll a subject that does not meet the eligibility criteria.

7. All major protocol exceptions must be approved by the NMDP IRB prior to implementation.

8. If a major protocol exception is implemented prior to NMDP IRB approval **to eliminate an immediate harm to a research subject (i.e., an emergency situation)**, the relying institution's investigator should assess the event to determine whether it could be considered an unanticipated problem involving risks to participants or others or potential serious or continuing non-compliance and then follow the appropriate reporting procedures, if applicable. (Refer to SOPs: S00407 *Unanticipated Problems Involving Risks to Participants or Others* and S00213 *NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements*.)

9. If a major protocol exception that does not involve an emergency situation is implemented prior to NMDP IRB approval, the event should be considered non-compliance, and the relying institution's investigator should follow the procedures in S00213 *NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements.*

10. If the same major protocol exception is requested more than once, it might not be granted by the NMDP IRB, and the IRB may request the submission of a protocol amendment.

11. **Requesting a major protocol exception:**

11.1. The relying institution's investigator must complete the *NMDP IRB Major Protocol Exception Request Form* and submit it via IRBManager.

11.2. If the relying institution has obtained approval for the major protocol exception request from the study sponsor or U.S. Food & Drug Administration (FDA) prior to IRB submission, documentation of such approval must be submitted with the IRB submission.

11.2.1. Major protocol exceptions involving an investigational device require prior approval by the sponsor and FDA. [21 CFR 812.150(4)]

11.3. If applicable, additional documents may be submitted with the *NMDP IRB Major Protocol Exception Request Form*, such as a subject information sheet or script of information to be conveyed to the subject.

11.4. The request for major protocol exception will be reviewed by the convened NMDP IRB. However, if the major protocol exception meets the criteria for expedited review, then the exception request will be reviewed via expedited procedures, and the IRB members will be notified of the review at the time of the next regularly scheduled IRB meeting.

11.5. The relying institution's investigator must maintain a copy of the IRB approval with the corresponding request for major protocol exception documentation in their study records.

MINOR PROTOCOL EXCEPTIONS

12. One example of a minor protocol exception would be scheduling a planned procedure or visit outside the protocol-required window to accommodate the subject's business travel.

13. Minor protocol exceptions do not require NMDP IRB approval prior to implementation.

14. Minor protocol exceptions must be documented by the investigator as part of their study records.

PROTOCOL DEVIATIONS

15. Protocol deviations may or may not affect the rights, welfare, or safety of the subject or the integrity of the study data. The NMDP IRB does not differentiate between "major" and "minor" protocol deviations.

16. **Examples of protocol deviations** include, but are not limited to:

16.1. Accidental failure to perform a protocol-required procedure, such as a physical or blood test

16.2. Failure to obtain a subject's written consent prior to performing a protocol procedure

17. When a protocol deviation is discovered, the relying institution's investigator should assess the event and determine whether it could be considered an unanticipated problem involving risks to participants or others or potential serious or continuing non-compliance, and then follow the appropriate reporting procedures, if applicable. (Refer to SOPs: S00407 *Unanticipated Problems Involving Risks to Participants or Others* and S00213 *NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements*.)

18. Protocol deviations must be documented by the investigator as part of their study records.

REPORTING PROTOCOL EXCEPTIONS AND DEVIATIONS AT THE TIME OF CONTINUING REVIEW

19. A list of major protocol exceptions, minor protocol exceptions, and protocol deviations that occurred since the study's last continuing review must be submitted to the NMDP IRB at the time of the study's next continuing review.

19.1. At a minimum, the list should include the information below. A template spreadsheet is available on the NMDP/Be The Match Network Website at the following link: https://network.bethematchclinical.org/research/institutional-review-board/sponsor/researcher-forms/

19.1.1. Study site where the protocol exception or deviation occurred

19.1.2. Date or time frame when the protocol exception or deviation occurred

19.1.3. Description of protocol exception or deviation

19.1.4. Classification (i.e., major protocol exception, minor protocol exception, or protocol deviation)

19.1.5. Whether or not the protocol exception was approved by the NMDP IRB prior to implementation

TEMPORARY VARIANCES

20. A temporary variance occurs when a sponsor or Study Chair wishes to make a systematic change to a previously IRB-approved protocol procedure prior to amending the protocol.

21. Usually, the reason for not amending the protocol at the time the variance is requested is because the sponsor/Study Chair wishes to wait until multiple protocol revisions can be

collected and can be made all at once to an amended protocol version at a pre-determined date. However, there may be other reasons for requesting a temporary variance; for example, in response to a public health crisis.

22. Examples of temporary variances might include, but are not limited to, a change in allowable visit windows, removal of a research test, a decrease in the volume of sample collection.

23. Temporary variances must be approved by the NMDP IRB prior to implementation.

24. To request NMDP IRB approval of a temporary variance, the sponsor/Study Chair must submit the Temporary Variance Request Form to the NMDP IRB. The sponsor/Study Chair should also attach their planned communication to participating study sites regarding the temporary variance.

25. The request for temporary variance will be reviewed by the convened NMDP IRB. However, if the temporary variance meets the criteria for expedited review, then the request will be reviewed via expedited procedures, and the IRB members will be notified of the review at the time of the next regularly scheduled IRB meeting.

26. The sponsor/Study Chair must receive NMDP IRB approval for the temporary variance prior to notifying participating study sites of the temporary variance.

27. It is anticipated that the next protocol amendment will include the changes approved for the temporary variance.

27.1. If the temporary variance is being requested in response to a public health crisis, and the sponsor/Study Chair does not intend to permanently amend the protocol, this should be explained in the Temporary Variance Request Form.

27.1.1. The sponsor/Study Chair must receive NMDP IRB approval prior to resuming normal protocol procedures.

REFERENCES

1. 21 CFR §56.108(a)(4)

2. 21 CFR 312.30(b)(2)(ii)

3. 21 CFR §812.150(4)

4. 45 CFR §46.103(b)(4) (Pre-2018 Requirements)

5. 45 CFR §46.108(a)(3)(iii) (2018 Requirements)

6. S00213 NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements

7. S00407 Unanticipated Problems Involving Risks to Participants or Others

Revision History

Revision	Brief Description of Revision
S00693 rev. 1	New SOP
S00693 rev. 2	Added definition, responsibilities and procedures for temporary variances. Added references.
S00693 rev. 3	Added definition of IRBManager. Added reference to IRBManager in 11.1.

ADDENDA

Not applicable