DAIDS Protocol Risk Ranking Data Capture and Distribution
Standard Operating Procedure

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Approval Date: April 11, 2016
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1.0 PURPOSE

The purpose of the DAIDS protocol risk ranking process is to ensure that site monitoring resources are allocated in a consistent and transparent manner utilizing a risk management based approach. This SOP describes the process for completing the DAIDS protocol risk ranking worksheet and entering the final protocol risk ranking level into the Clinical Site Monitoring (CSM) System of the NIAID Clinical Research Management System (NCRMS). The entry of the risk level (1-3) in the CSM System will help determine the percentage of PIDs to be selected for informed consent, eligibility verification and record review during clinical site monitoring.[1] For protocols undergoing courtesy review, or if DAIDS does not take responsibility as funder, sponsor or monitor for safety, a code of ninety-nine (99) will be recorded in the CSM, which is equivalent to no monitoring.

2.0 DEFINITIONS

- **Protocol Risk Coordinator (PRC):** The person who is responsible for receiving the submitted Protocol Risk Worksheet and generating a risk score and risk level. This person will also be responsible for tracking and requesting worksheets that are past due for risk ranking.

- **Protocol Risk Worksheet:** A one-page questionnaire designed to rank protocols according to risks to the study participant and data integrity (see Attachment 1).

- **Risk Guidelines:** Directions (guidance) for the Protocol Medical Officer (MO) / Program Officer (PO) for completing the Protocol Risk Worksheet (see Attachment 2).

- **Risk score:** A score ranging from 1-100 generated according to responses to the Protocol Risk Worksheet questions.

- **Risk level:** Levels ranging from 1-3, allocated according to the risk score. The risk level is used to determine the extent of monitoring of clinical records (see Figure 1). Protocols not being monitored will also be tracked.

[1] The protocol risk worksheet needs to be filled out for all protocols with the exception of a sub-study. A sub-study usually acquires the same risk level as its main study, however, the protocol risk coordinator will communicate with Programs to find out if a sub-study should inherit the same risk level as its main study and if it will be monitored or not.

Figure 1. Risk Scores and Associated Risk Levels

Risk-Based Ranges of Monitoring

Risk Score	*Risk Level	**IC/EC Review	Record Review
56-100	1	50-100%	25-50%
31-55	2	20-50%	15-30%
1-30	3	10-20%	10-20%

3.0 PROCEDURES

(See Attachment 4 for protocol risk ranking work flow diagram.)

3.1 Distribution of Protocol Risk Worksheet:

3.1.1 The DAIDS Regulatory Support Center (RSC) Scientific Review Committee (SRC) Coordinator will distribute the Protocol Risk Worksheet with pre-populated fields abstracted from the protocol (Protocol DAIDS Number, Version Number, Total Sample Size, and the Protocol Title) in the email notification for the final SRC meeting for the respective protocol.

3.1.2 Upon receipt of the RSC email notification, the DAIDS Protocol Risk Coordinator (PRC) will record the name of the Protocol MO/PO, Protocol DAIDS Number e.g., A5230/10152, SRC Review date, and expected worksheet submission date in the Protocol Risk Worksheet Tracking spreadsheet.

4.0 COMPLETION OF THE PROTOCOL RISK WORKSHEET

4.1 Within 10 business days following the final SRC review, the Protocol MO/PO will:

4.1.1 Complete the Protocol Risk Worksheet, consulting with relevant OPCRO staff as needed.

4.1.2 Review the completed Protocol Risk Worksheet with their Branch Chief or designee as needed.

4.1.3 Submit the completed worksheet to the PRC.

4.2 An email confirmation will be sent from the PRC following a submission of a Protocol Risk Worksheet.

4.3 In the event that a worksheet is not received, the PRC will send automated email reminders that the Worksheet is due 7 and 10 business days post final SRC meeting. The email reminders will have a "read receipt" and the appropriate Branch Chief will be copied.[2]

5.0 PROTOCOL RISK SCORE CALCULATION AND RISK RANKING

5.1 Upon receipt of the completed Protocol Risk Worksheet the PRC will:

5.1.1 Record the date of receipt in the Protocol Risk Data spreadsheet.

5.1.2 Import the data from the worksheet into the Protocol Risk Data spreadsheet to calculate the protocol risk score and corresponding risk level.

5.1.3 Send risk level email notification (Attachment 3) to the protocol MO/PO and OCSO Monitoring Operations Branch (MOB), and record sent date in the Protocol Risk Data spreadsheet.

6.0 OCSO RECEIPT AND PROCESSING OF THE RISK LEVEL

An overview flow chart of the entire risk ranking process is located in Attachment 4.

7.0 RE-ASSESSING PROTOCOL RISK

The protocol MO/PO will be responsible for determining whether an amended protocol with significant protocol revisions should undergo SRC. In preparation of SRC and based on established procedures, the protocol risk worksheet will be re-distributed by the RSC for re-assessment of the protocol by the MO/PO. The MO/PO may elect to submit another worksheet to re-assess an amended protocol not undergoing SRC.

8.0 ATTACHMENTS

Attachment 1: Protocol Risk Worksheet
Attachment 2: Protocol Risk Worksheet Guidelines
Attachment 3: Calculated Protocol Risk Level E-mail Notification to Medical Officer
Attachment 4: Protocol Risk Ranking Flow Diagram

[2] Notify the Protocol Risk Coordinator at plummerjr@niaid.nih.gov or at 240-292-4691 should you have a computer technical issue that prohibits you from completing the Protocol Risk Worksheet electronically.

Attachment 1: Protocol Risk Worksheet

Division of AIDS (DAIDS) Protocol Risk Worksheet

Protocol DAIDS # | Version # | Total Sample Size

Protocol Title

---- To be completed by the DAIDS Medical Officer (MO) ---- | To access the Protocol Risk Worksheet Guidelines, please click here

Please note that blue text has a pop-up definition for all enabled (non-grey) questions.

Protocol MO Name | MO Completion Date (use DD-Mon-YYYY or click down arrow for calendar)

☐ Initial Assessment ☐ Reassessment

1. Protocol Information

1.1. Will the clinical sites be monitored by a non-DAIDS entity (i.e., other than DAIDS Monitoring Contract)? ☐ Yes ☐ No ☐ Decision is pending

1.2. Will this protocol be risk ranked? ☐ Yes ☐ No

1.3. Is this a Clinical Trial? ☐ Yes ☐ No

1.4. Select Study Risk Category: ☐ Minimal Risk ☐ Greater than Minimal Risk

1.5. In general, minimal risk studies are not monitored. Is an exception recommended to request monitoring of this minimal risk study?

☐ Yes

☐ No

1.6. Highest Phase of the study:

☐ NA
☐ Phase I, Ib
☐ Phase II, IIa, IIb (for therapeutic studies, including therapeutic vaccines) and II/III
☐ Phase III, IIb (for vaccine and prevention studies) and III/IV
☐ Phase IV (study product approved by FDA for indication and population)

1.7. IND/IDE status:
Are data intended to be used for a regulatory purpose (such as submission to an IND/IDE or NDA), or to alter standard of care recommendations? ☐ Yes ☐ No

1.8. Level of potential harm/toxicity related to intervention within the study population:

☐ Low ☐ Moderate ☐ High

2. Human Subjects Protection

2.1. Will the protocol have any Vulnerable Populations? ☐ Yes ☐ No

2.2. Are there additional privacy/confidentiality concerns? ☐ Yes, Low ☐ Yes, Moderate to High ☐ No

3. Study Complexity

3.1. Level of study design complexity: ☐ Low ☐ Moderate to High

3.2. Study visit intensity: ☐ Low ☐ Moderate ☐ High

4. Additional Factors

4.1. Specify factors to be considered for possible adjustment up or down of the priority level for the study:

☐ No additional factors ☐ Non-network study

4.2. Other issues - Specify and/or Notes to OCSO (below):

Version 2.1 Date: 02MAY16 | Reset Form | Submit

Attachment 2: Division of AIDS Risk Worksheet Guidelines

The worksheet is designed to assign risk levels to protocols for prioritizing clinical site monitoring resources. To ensure consistency of responses, please refer to the following guidelines while completing the worksheet.

Note: For the ease of the user, blue text on the worksheet will have a visible definition, explanation, or guidance associated with it when hovering over it with your cursor. However, if a section of the worksheet is greyed out/inactive, you will not be able to hover over blue text until that section is activated. Also, if prompted, please close out of all Adobe update notifications as only IT can update programs on NIAID DAIDS computers.

While the top section of the form will be pre-populated by Regulatory Support Contractor (RSC) personnel, please ensure that you complete the fields: MO Name and **MO Completion Date** and indicate whether this is an Initial Assessment or a Reassessment of a protocol before completing other sections of the Worksheet.

Logic checks have been programmed into the form. Based on the selection of an answer to a question, subsequent questions that are not applicable are greyed out and do not require completion. Remember to press the submit button at the bottom of the form once all information has been entered.

COMPLETITION INSTRUCTIONS FOR PROTOCOL RISK WORKSHEET

1. PROTOCOL INFORMATION

1.1. Will the clinical sites be monitored by a non-DAIDS entity (i.e., other than DAIDS Monitoring Contract)?

- o Yes
- o No
- o Decision is pending

1.2. Will this protocol be risk ranked?

- o Yes
- o No – This protocol will not be risk ranked because it is a protocol submitted for courtesy review or because DAIDS does not take responsibility as funder, sponsor, or clinical/safety monitor.

1.3. Is this a Clinical Trial?

Definition: A prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, devices, or new ways of using known treatments to determine whether they are safe and effective. (DAIDS Glossary).

- o Yes
- o No

1.4. Select Study Risk Category?

- o Minimal Risk – Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303 (d)).
- o Greater than Minimal Risk – Greater than minimal with Minimal Risk being defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303 (d))

Attachment 2: Division of AIDS Risk Worksheet Guidelines

1.5. In general, minimal risk studies are not monitored. Is an exception recommended to request monitoring of this minimal risk study?

- o Yes→ Provide justification
- o No → **Stop – Submit form now.**

1.6. Highest Phase of the study:

For interventional studies for which there is no phase, check NA

- o NA
- o Phase I, Ib
- o Phase II, IIa, IIb (for therapeutic studies, including therapeutic vaccines) and II/III
- o Phase III, IIb (for vaccine and prevention studies) and III/IV
- o Phase IV (study product approved by FDA for indication and population)

Definitions:

- Phase I: Studies that are usually conducted with healthy volunteers and that emphasize safety. The goal is to find out what the drug's most frequent and serious adverse events are and, often, how the drug is metabolized and excreted.
- Phase II: Studies that gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short- term adverse events are studied.
- Phase III: Studies that gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs.
- Phase IV: Studies occurring after FDA has approved a drug for marketing. These include postmarket requirement and commitment studies that are required of or agreed to by the sponsor. These studies gather additional information about a drug's safety, efficacy, or optimal use.

1.7. IND/IDE status:

If needed, refer to protocol title page, Protocol Management (quick summary), or refer to RAB. Are data intended to be used for a regulatory purpose (such as submission to an IND/IDE or NDA), or to alter standard of care recommendations?

- o Yes
- o No

1.8. Level of potential harm/toxicity related to intervention within the study population:

- o Low
- o Moderate
- o High – Specify

Definitions:

- Low potential for harm/toxicity – Safety profile well-described for the target population and mild/infrequent harm/toxicities expected overall, resulting in a highly favorable intervention risk/benefit ratio for the indication/population being studied. Life- threatening adverse events may be possible, but clearly occur only rarely.

Examples:

Treatment interventions: As expected with a well-established, first-line ARV combination in the usual adult or pediatric clinic population.
Prevention interventions: Overall minimal harm/toxicities expected based on a very substantial amount of accumulated experience.

- Moderate potential for harm/toxicity – Safety profile for target population is not fully described (is under continued investigation) and/or moderate to severe grade harm/toxicities may be expected at moderately higher rate than for standard low risk interventions. Risk/benefit ratio is not as favorable, but still clearly acceptable for the indications/population being studied.

  Examples:

  Treatment interventions: Mild to severe adverse events may be expected to occur at a moderately higher frequency than for a well-established, first-line ARV combination, but life-threatening AEs expected to be rare.
  Prevention/vaccine interventions: Early stage evaluation of new agents that could potentially have more than minimal harm based on (limited) existing data.

- High potential for harm/toxicity – Safety profile for the target population not yet described and/or moderate-to-severe or life-threatening harm/toxicity expected at a substantially higher rate than for low risk/standard interventions. Risk of harm is high but justified by expected benefit, or risk/benefit ratio is not yet established as clearly favorable for the population/indication being studied.

  Examples:

  Treatment interventions: Moderate to severe adverse events may be expected to occur substantially more frequently than with a well-established, first line ARV therapy and/or life-threatening events are expected to occur more frequently than rarely based on existing evidence. Also, first-in-human trials or only minimal safety data are available.

  Treatment and Prevention interventions: Generally applicable only to first-in-human trials or very early stage evaluations with minimal available safety data.
  (Continue to next)

2. HUMAN SUBJECTS PROTECTION

2.1. Will the protocol have any Vulnerable Populations?

Definition: Persons in a hierarchical structure or anyone who has compromised capacity for free consent because they are easy to manipulate as a result of their illness or socioeconomic condition. Examples include: children, prisoners, pregnant women, refugees, cognitively impaired, terminally ill, elderly, soldiers or students. (ICH E-6 and the OHRP IRB guidebook)

- o Yes
- o No

2.2. Are there additional privacy/confidentiality concerns?

- o Yes, Low – Concerns associated with standard clinical care or participation in any clinical trial.
- o Yes, Moderate to High – Research involving illegal behavior or questionnaires dealing with sensitive personal information.
- o No

Attachment 2: Division of AIDS Risk Worksheet Guidelines

3. STUDY COMPLEXITY

3.1. Level of study design complexity:

- Low – No placebo, may include no more than one randomization, may include two steps/phases/cohorts.
- Moderate to High - Use of placebo, more than one randomization (e.g. factorial design) and/or more than two steps/phases/cohorts; studies with multiple types of study populations (e.g. mothers and infants, HIV discordant couples); complex study agent administration/management.

3.2. Study visit intensity

What is the most intense study visit after the baseline/entry visit?

- Low – Only routine/non-intensive evaluations – For example: Un-timed blood draws; non- invasive sample collection/testing; simple, non-invasive imaging procedures; brief/simple questionnaires.
- Moderate – 1-2 non-routine evaluations – For example: Timed or invasive sample collections/testing; time-intensive imaging procedures; complex questionnaires; evaluations requiring coordination with multiple departments.
- High – More than 3 non-routine evaluations – For example: Time or invasive sample collection/testing; time-sensitive imaging procedures; complex questionnaires; coordination with multiple departments; OR any protocol mandated hospitalizations.

4. Additional Factors

4.1. Specify factors to be considered for possible adjustment up or down of the priority level for the study:

- No additional factors
- Non-network study

Other issues – Specify and/or Notes to OCSO (in the available space below)

This section of the form is accessible at all times to allow highlighting specific issues and adding notes to OCSO.

INSTRUCTIONS FOR SUCCESSFULLY SUBMITTING COMPLETED WORKSHEET

- Click "**Submit**" located at the bottom of the worksheet
- When the **Select Email Client** pop-up window appears, select "**Desktop Email Application**"
- Click "**OK**"

After you click "OK", your completed worksheet will automatically go to the Outlook inbox of the Protocol Risk Coordinator who is Jennifer Plummer and an automatic notice will generate and be sent to your email address that your worksheet has been successfully submitted for processing. Within two (2) business days the Protocol Risk Coordinator will send you an email with your protocol risk level.

You also have the option to reset the Worksheet.

Attachment 3: Calculated Protocol Risk Level Email Notification to Medical Officer/Program Officer and OCSO MOB

Dear Dr. Piper,

Thank you for the submitted Protocol Risk Worksheet. Based on the information provided, your protocol Risk Level is indicated below

Protocol Number	Risk Level
MTN-033/IPM 044	**1**

The Risk Level of the protocol corresponds to the level of clinical site monitoring below.

Risk Level	Informed Consent/ Eligibility Criteria Review	Record Review
1	50-100%	25-50%
2	20-50%	15-30%
3	10-20%	10-20%
Note: Although all DAIDS sponsored studies presented at SRC are required to be risk ranked, there might be some instances when the study has almost very low or no risk factors to DAIDS, and it could possibly be deemed as **"No monitoring"** in the DAIDS-ES Clinical Site Monitoring (CSM) system.		

Please contact your OCSO Liaison if you have any questions.

Jennifer Plummer[c]
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Attachment 4: DAIDS Protocol Risk Ranking Process Flow Diagram