1. PURPOSE

1.1 The purpose of this policy is to describe when a Statistical Analysis Plan (SAP) is necessary for DMID-funded clinical trials.

2. SCOPE

2.1 This policy pertains to:

- Clinical Trials conducted under DMID-held Investigational New Drug Applications (IND) or Investigational Device Exemptions (IDE).
- Non-IND/IDE Clinical Trials funded by contract or cooperative agreement.

3. DEFINITIONS

3.1 Statistical Analysis Plan (SAP) - A SAP is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. (ICH E9)

For additional definitions, see DMID glossary.

4. RESPONSIBILITIES

4.1 As described in policy.

5. POLICY

5.1 All DMID-funded clinical protocols must describe the principal features of any statistical methods to be employed and any planned interim analysis.

5.2 A stand-alone SAP that provides full details about the proposed statistical analyses and includes details of the primary summary tables and graphs anticipated for the final statistical report is required for the clinical trials defined below.

5.2.1 All phase 2, 3, and phase 4 clinical trials or device clinical trials.

5.2.2 Any clinical trial or device trial with efficacy outcomes as a primary or secondary endpoint.

- When an established surrogate is used for an efficacy endpoint, it is considered an efficacy endpoint when determining if an SAP is required.

5.2.3 An SAP may be required for other clinical trials based upon DMID's assessment, as conveyed by the Contracting Officer's Representative (COR) or Program Officer (PO).

5.2.4 For other clinical trials not meeting criteria 5.2.1-5.2.3 above including phase 1 trials, the investigator the investigator(s) and study team (if applicable) should consider how planned analyses are conveyed.

- An SAP may be used for these trials.

- If there is no SAP being used, the Statistical Considerations section of the protocol should describe any statistical analyses that will be performed including interim analyses, in enough detail to be able to reproduce the analyses, and define the analysis populations (*e.g.,* intention-to-treat or per-protocol) in which they will be performed.

5.3 The SAP must contain details about any planned interim analyses.

5.4 The SAP must contain all primary and secondary endpoints listed in the protocol.

5.4.1 Secondary analyses based on data that will be available at a time well past the primary analysis may be better in a separate or addendum SAP (to clearly describe what will be in the main CSR and an addendum CSR).

5.5 The SAP must list all exploratory endpoints and note if the planned analyses are part of the SAP.

5.5.1 Exploratory endpoint analyses should be included in the SAP if the data is intended to be submitted to regulatory authorities and potentially used for regulatory decisions.

5.5.2 Except as listed in 5.5.1, exploratory endpoint analyses don't need to have formal analyses prespecified in the SAP. The decision on which exploratory endpoint analyses to include in the SAP may be made by the protocol team.

- Exploratory endpoint analyses not included in the SAP must be so noted to convey the intent to the reader.

5.6 For analyses that go beyond single endpoint results (e.g., proteomics, virus sequencing, etc.), the SAP may reference a separate document that describe the analyses.

5.7 The SAP must be finalized and submitted to the FDA/regulatory agencies if the trial is under an IND, IDE, or international equivalent, before conducting any interim analyses or breaking the blind (*i.e.,* identifying the treatment assignment).

5.7.1 For DMID sponsored IND trials, the assigned Regulatory Affairs Manager (RAM) will determine the waiting period for FDA review of the SAP on a case-by-case basis. FDA's recommended timeline for evaluating an SAP is up to 60 days but may be adjusted depending on the complexity of the submitted material, public health needs, and other factors.

6. REFERENCES

6.1 International Conference of Harmonization (ICH) Guideline E6(R2), "Good Clinical Practice": https://www.fda.gov/media/93884/download

6.2 International Conference of Harmonization (ICH) Guideline E9, "Statistical Principals for Clinical Trials": https://www.fda.gov/media/71336/download

6.3 FDA Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry: https://www.fda.gov/media/164960/download

6.4 FDA Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review: https://www.fda.gov/media/85790/download

7. APPENDICES

Not applicable

8. REVISION HISTORY

8.1 This version replaces REG-Policy-007 and was edited at the time of incorporation into the eQMS.

9. ADDITIONAL INFORMATION

9.1 Document Lead: Associate Director of Clinical Research (ADCR)

9.2 Posting externally: Yes