**INSTRUCTIONS FOR USING**

**THE**

**DMID SAMPLE REGULATORY FILE REVIEW TOOL**

**Background**: This protocol-specific Regulatory File Review Tool is based upon the International Council for Harmonisation Guidelines for Good Clinical Practice (ICH GCP E6(R2)), the Code of Federal Regulations Title 45 Public Welfare Part 46 Protection of Human Subjects, Code of Federal Regulations Title 21 Parts 50, 54, 312, 812, and the [DMID Regulatory File Document Guidelines](https://www.dmidcroms.com/SitePages/Guidelines.aspx).

**How to use this tool**: This tool may be used to guide and document sites’ internal quality review of the Regulatory File for each individual protocol conducted at the site. This tool uses Microsoft Word and is modifiable, as needed, to reflect applicable protocol, sponsor and site essential document requirements, and site IRB requirements. Three time points are recommended for effective Regulatory File review; *prior to initiation of protocol activities, during* *the active study period*, *and at study close out.*

For each Regulatory File reviewed:

1. **Complete**: Begin using this tool by completing the header information (name of site, name of reviewer, date of review, and the protocol number) for the protocol being reviewed.
   1. For each section reviewed, check the appropriate boxes (‘N/A’, ‘Yes’, or ‘No’).
   2. If the ‘No’ box is checked for any question, provide a description for each ‘No’ response in the area provided within that section.
2. **Apply** **Document** **Version Control**: When adopting and modifying this tool for discretionary use, correct the footer to reflect version control. Please refer to the [DMID Information Sheet; Document Version Control Guidelines](https://www.dmidcroms.com/Shared%20Documents/Document%20Version%20Control%20Guidelines%20Info%20Sheet.pdf#search=document%20version%20control%20guidelines).
3. **Summarize**: At the conclusion of the review, summarize findings in the Summary of Findings section. These summaries are a useful reference when completing a Quality Management Summary Report.
4. **Sign and Date**: The site’s quality reviewer signs and dates the Regulatory File Review Tool
5. **File and Maintain**: File all versions of the site’s CQMP and associated documents/tools in the site’s Quality Management File.
6. **Resolve Findings and Follow Up**: Follow your site/protocol-specific Clinical Quality Management Plan regarding communication and resolution of findings from internal Regulatory File reviews. Site Regulatory File reviews are independent of clinical site monitoring visits.

**Resources:**

DMID Clinical Quality Management Plan Policy:

<https://www.niaid.nih.gov/sites/default/files/qualitymgmtplan.pdf>

DMID Clinical Research Resources – Source Documentation Standards

<https://www.dmidcroms.com/SitePages/Guidelines.aspx>

DMID Regulatory File Document Guidelines

<https://www.dmidcroms.com/SitePages/Guidelines.aspx>

U.S. Food and Drug Administration E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry

<https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf>

ICH Guideline for Good Clinical Practice E6(R2)

<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>

Office of Human Research Protections (OHRP) Code of Federal Regulations Title 45 Part 46:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

U.S. Code of Federal Regulations 21 CFR 50 Protection of Human Subjects

<http://www.ecfr.gov/cgi-bin/text-idx?SID=9a408393b6ad93ddb9d3309e5e5a3b62&mc=true&tpl=/ecfrbrowse/Title21/21cfr50_main_02.tpl>

U.S. Code of Federal Regulations 21 CFR 54 Financial Disclosure by Clinical Investigators

<http://www.ecfr.gov/cgi-bin/text-idx?SID=9a408393b6ad93ddb9d3309e5e5a3b62&mc=true&node=pt21.1.54&rgn=div5>

U.S. Code of Federal Regulations 21 CFR 312 Investigational New Drug Application

<http://www.ecfr.gov/cgi-bin/text-idx?SID=9a408393b6ad93ddb9d3309e5e5a3b62&mc=true&node=pt21.5.312&rgn=div5>

U.S. Code of Federal Regulations 21 CFR 812 Investigational Device Exemptions

<http://www.ecfr.gov/cgi-bin/text-idx?SID=9a408393b6ad93ddb9d3309e5e5a3b62&mc=true&node=pt21.8.812&rgn=div5>

U.S. Food and Drug Administration Guidance for Industry – Computerized Systems Used in Clinical Investigations

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computerized-systems-used-clinical-investigations>

U.S. Food and Drug Administration Guidance for Industry – Electronic Source Data in Clinical Investigations

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf>

U.S. Food and Drug Administration Guidance for Industry – Use of Electronic Health Record Data in Clinical Investigations <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf>

**DMID SAMPLE REGULATORY FILE REVIEW TOOL**

<*Replace DMID SAMPLE with Institution/Site Name*>

Reviewer: <*Name of person reviewing regulatory file*> Review Date: <*Date of regulatory file review*>

Protocol Number: <*DMID Protocol Number*>

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| **Form FDA 1572 / Investigator of Record (IOR) Agreement** | | | |
| 1. | Is a Form FDA 1572 (for IND studies) or an IOR (for non-IND studies) on file? | Yes | No |
| 2. | Is the agreement version current and accurate? | Yes | No |
| 3. | Does the agreement include a hand-written signature and date by the Principal Investigator? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Study Personnel Signature / Responsibility List** | | | |
| 1. | Does the Study Personnel Signature / Responsibility List contain all study personnel, including those who are making entries or corrections on the case report forms, as well as all ancillary study personnel? | Yes | No |
| 2. | Does the Study Personnel Signature / Responsibility List contain the name, title, signature, initials, delegated tasks, phone number, e-mail address, start date, and end date for each study staff member listed? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Protocol** | | | | |
| 1. | Is a current and valid copy of the IRB-approved protocol on file? Version #: \_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | Yes | No |
| 2. | Are all previous versions of the protocol on file? | | Yes | No |
| 3. | For protocols with a Protocol Signature Page, is it complete, signed, and dated by the Principal Investigator? | | Yes | No |
| 4. | For multi-center studies, is the Protocol Signature Page from the site Principal Investigator on file? | N/A | Yes | No |
| For each “no" response, provide a description: | | | | |

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| **Informed Consent Form(s) (ICFs)** | | | |
| 1. | Is a current and valid (IRB/IEC-approved) copy of the Informed Consent Form on file? Version #:\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Yes | No |
| 2. | Are all previous versions of the Informed Consent Form on file? | Yes | No |
| 3. | If applicable, are other consent forms (current and previous versions) on file? For example: assent forms, short forms, screening consents, or future use consents. | Yes | No |
| For each “no” response, provide a description: | | | |

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| **IRB/IEC Approvals and Final Reports** | | | | |
| 1. | Does the file contain a current Regulatory Review History Form or IRB equivalent form?  **Note: Review site regulatory history against IRB regulatory history**. | N/A | Yes | No |
| 2. | Is the initial IRB/IEC approval for the protocol and the ICF present? Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Are all IRB/IEC approvals on file for advertisements, recruitment/telephone scripts, and participant information materials? | | Yes | No |
| 3. | If applicable, are subsequent approvals present? Include Continuing / Annual Reviews, and amendments. | N/A | Yes | No |
| 4. | Do the IRB/IEC approval letters include the full protocol title and list all study documents (identified with version number/date) that were reviewed? | | Yes | No |
| 5. | Does the IRB/IEC documentation include the date of approvals and/or duration of approval? Expiration date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | Yes | No |
| 6. | If a lapse in IRB/IEC approval has occurred, is it documented properly?  **Note: A lapse in IRB/IEC approval requires IRB/IEC and DMID notification.** | N/A | Yes | No |
| 7. | Are periodic reports to the IRB/IEC present? If not, where are they located? | N/A | Yes | No |
| 8. | If applicable, is the Final Report to the IRB/IEC present? | N/A | Yes | No |
| 9. | If applicable, is the Final Report to the sponsor present? | N/A | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **IRB/IEC Composition** | | | | |
| 1. | Is a current IRB/IEC Roster or Membership composition on file? If the IRB/IEC does not provide a roster, is a letter on file stating the names are not released and the IRB/IEC is in compliance with 45 CFR 46 regulations? | | Yes | No |
| 2. | If any site personnel are members of the IRB/IEC; is there documentation that the member absented from voting on this protocol? | N/A | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **Study-specific Procedures / Manual of Procedures** | | | |
| 1. | Does the file contain the current approved study-specific procedures or the Manual of Operational Procedures (MOP) with version and date? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Screening / Enrollment Log** | | | |
| 1. | Is the Screening/Enrollment Log present and current? | Yes | No |
| 2. | For all ineligible subjects, is the reason for ineligibility documented on the Screening/Enrollment Log? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **ID Code List** | | | |
| 1. | Is the ID Code List present and up to date for all enrolled subjects? | Yes | No |
| 2. | Is the ID Code List stored in a secure location separate from where source documents and personal identifiers are maintained? Include the location of the ID Code List in the regulatory file. | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Study Product (Should be performed ONLY by unblinded personnel if study is blinded)** | | Not applicable | | |
| 1. | Is a sample study product label on file? | | Yes | No |
| 2. | Is the study product accountability record accurate, current, and on file? Does it agree with the actual inventory on hand? | | Yes | No |
| 2a. | Is disposition of used and unused study products captured on the accountability logs? | | Yes | No |
| 3. | Are instructions (protocol-specific MOP) for the storage, mixing, and handling of study product on file and easily accessible? | | Yes | No |
| 4. | Do shipping records for study product document the receipt date, quantity, temperature, and lot numbers of all study products on file? | | Yes | No |
| 5. | Are the randomization list and decoding procedures for blinded study product on file? | | Yes | No |
| 6. | Are study product temperature logs on file? (includes receipt and storage) | | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **Specimen Retention –** Refer to the current protocol and Manual of Operational Procedures (MOP). | | Not applicable | | |
| 1. | Are specimen retention records on file? | | Yes | No |
| 2. | Are research specimen temperature logs on file? | |  |  |
| 3. | Are shipping documents accurate and complete?  **Note: Global Trace, EMMES Missing Specimens Report, Shipping Logs, Shipping Receipts, etc.** | | Yes | No |
| If “no”, provide a description of the issue(s): | | | | |

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| **Serious Adverse Events (SAEs) / IND Safety Reports** | | | | |
| 1. | Are all SAEs reported to the DMID and IRB/IEC present in the file? | | Yes | No |
| 2. | Are IND Safety Reports/Memos for this protocol on file? | N/A | Yes | No |
| 3. | Is documentation on file for IND Safety Reports submitted to the site/institution IRB/IEC? | N/A | Yes | No |
| For each no response, provide a description: | | | | |

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| **Protocol Deviations** | | | |
| 1. | Are all protocol deviations documented and on file? | Yes | No |
| 2. | Were all protocol deviations submitted to DMID and site/institution IRB/IEC per its guidelines?  **Note: Protocol Deviation submission may be required by other sponsor data collection entities such as EMMES, etc.** | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Investigator Brochures (IB) / Package Inserts** | | | Not applicable | | |
| 1. | Are all versions of the IBs for investigational products present, current, and available? | | | Yes | No |
| 2. | If applicable, are package inserts present, current, and on file for approved drugs? | N/A | | Yes | No |
| 3. | Is documentation on file for IB and/or package inserts submitted to the IRB? | | | Yes | No |
| For each no response, provide a description: | | | | | |

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| **Laboratory Normals and Accreditations** [DMID CROMS Laboratory Essential Regulatory Documents](https://www.dmidcroms.com/CRS/ERDG/EssentialRegulatory/CROMS%20ERDG%20Laboratory%20Information%20Sheet.pdf#search=DMID%20CROMS%20laboratory%20essential%20regulatory%20documents) specifies DMID requirements regarding laboratory facility accreditation applicable to the protocol and associated recordkeeping in the study essential regulatory files. This guidance is accessible on the DMID CROMS Web Library. This section should be amended to reflect accurate site information for quality review of Laboratory Essential Regulatory Documents consistent with the appropriate laboratory facility/setting, tests, documentation of accreditation, and normal/reference ranges applicable to the protocol. Laboratory recordkeeping applies to DMID Clinical Central Laboratory, Clinical Laboratories, Research Laboratories, Point of Care Testing Certificates of Waiver, Laboratory Confirmatory Testing, Safety Labs (including lab work, blood work, eligibility testing, screening, baseline testing, post-exposure testing).  Not applicable | | | | |
| 1. | Are laboratory certifications and accreditations present for DMID central and/or U.S. clinical laboratories? (i.e., CAP and CLIA Accreditation, Certificate of Waiver.) | | Yes | No |
| 2. | Are applicable non-US equivalent certificates of qualification for the laboratory on file? If no certification or qualification provided, is a statement included explaining the reason, and a description of the standard being used? | N/A | Yes | No |
| 3. | Are Laboratory Normal Ranges for all protocol-required tests on file? Documentation must include all clinical and safety laboratory tests required by the protocol, the unit of measure, the laboratory name/address, and the date of the document. | N/A | Yes | No |
| 4. | For IND studies, does the Form FDA 572 include the name and address of all clinical laboratory facilities to be used in the study? | N/A | Yes | No |
| 5. | For non-IND studies, does the Investigator of Record form include the name and address of all clinical laboratory facilities to be used in the study? | N/A | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **Sample Case Report Forms** | | | |
| 1. | Are final (actually used) versions of the sample CRFs / eCRFs, subject diaries, or other forms used for documenting/entering data, on file? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Curricula Vitae (CVs) and Medical Licenses** | | | |
| 1. | Are CVs present for the Principal Investigator and sub-investigators listed on the Form FDA 1572 / Investigator of Record (IOR)? | Yes | No |
| 2. | Are the CVs current (within 5 years of the current date)? | Yes | No |
| 3. | Are the medical licenses present and current for the Principal Investigator and sub-investigators listed on the Form FDA 1572 / IOR? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Financial Disclosure (applicable for DMID IND studies only)** | | Not applicable | | |
| 1. | Are financial disclosure forms for all personnel listed in Section 1 and Section 6 of the Form FDA 1572 present on-site?  **Note: These forms should not be filed in the site’s regulatory file, but in a separate location.** | | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **Federal Wide Assurances (FWA)** | | | |
| 1. | Is the current FWA document from Office of Human Research Protections (OHRP) present? Is the expiration date present? Expiration Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Yes | No |
| 2. | Is the IRB/IEC approving this protocol registered with OHRP and linked with this FWA? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Local and Foreign Regulatory Approvals** | | | | |
| 1. | Are all local, state, and/or special authorizations related to the protocol maintained and up to date? (related to Study Product, Special Populations, Legally Authorized Representatives consenting) | | Yes | No |
| 2. | If this is a non-U.S. site, is documentation of foreign regulatory body approval or clearance on file? | N/A | Yes | No |
| For each “no” response, provide a description: | | | | |

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| **Site Monitoring Log and Reports** | | | |
| 1. | Are copies of Site Monitoring Logs and Site Monitoring Reports on file? (Assessment, Initiation, Interim Monitoring, Close-out) | Yes | No |
| For each “no" response, provide a description: | | | |

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| **Sponsor Correspondence** | | | |
| 1. | Are all correspondences between the site and sponsor on file? | Yes | No |
| 2. | Is the Site Activation memo on file? | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Internal Correspondence** | | | |
| 1. | Does the file contain all up-to-date internal correspondence? (i.e. Clinical, Laboratory, Pharmacy, Radiology, etc.) | Yes | No |
| For each “no” response, provide a description: | | | |

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| **Notes to the Study File** | | | | |
| 1. | Does the file contain study-specific notes to file? | | Yes | No |
| 2. | Are the notes to file completed in accordance with the DMID guidelines?  **Note: The DMID guidelines, Information Sheet *Writing Notes to the Study File* is provided on the** [**DMID-CROMS Web Library**](https://www.dmidcroms.com/SitePages/Guidelines.aspx) | | Yes | No |
| 3. | Have all notes to file been forwarded to DMID as per the DMID guidelines? | N/A | Yes | No |
| For each no response, provide a description: | | | | |

**Summary of Findings:** < Provide a summary of accumulated issues / adverse trends detected and documented during internal quality reviews. Additionally, where applicable, summarize corrective actions / preventive action planning, inclusive of timelines and follow-up evaluation for effectiveness, as described in the CQMP.

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Reviewer Title: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Signature: ­­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: <insert DD/MMM/YYYY>

<Note: Reviewer title/signature as provided on the Study Personnel Signature-Responsibility List / Delegation of Responsibility Log>