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| The purpose of this checklist is to provide support for Research Compliance Specialist or IRB members/ Designee. This checklist must be used if the Investigator in the proposed research project is also the IND Holder. The IRB in conjunction with others within the Human Research Protection Office (HRPO) will evaluate whether the investigator is knowledgeable about the requirements and follows them while conducting the study. **HRPO may require additional oversight and monitoring to ensure compliance with sponsor-investigator requirements.** | | |
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| **General Responsibilities for Sponsor-Investigator** | | |
| **IRB Protocol Number** | | |
| **Principal Investigator** | |  |
| **IRB Protocol Number** | |  |
| **IND Holder** | |  |
| **IND number** | |  |
| **Date Checklist Completed** | |  |
| **Person completing the checklist** | |  |
| **Date checklist completed** | | |
| 1. Maintain an effective IND with respect to the investigation *21 CFR 312.50 (Sponsor*) | | |
| Yes  No | Original IND Application (Form FDA-1571 and accompanying documentation for the initial investigational new drug (IND) application, including: cover letter, protocol, chemistry, manufacturing, and controls data, FDA letter of no objection, Documentation of IND#) | |
| Yes  No  N/A | Notify the FDA of new protocols using the same IND, change in protocol, new investigator, new information, safety reports, annual reports[[1]](#endnote-1), response to FDA request for information, changes in financial disclosure, and general correspondence. | |
| Yes  No  N/A | Updated Form FDA-1572 when there is a new investigator | |
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| 1. Transfer of obligations to a contract research organization *21 CFR 312.52 (Sponsor*)  N/A | | |
| Yes  No | Describe in writing the obligations that have been transferred to a CRO | |
| Yes  No | Provide contract with CRO | |
| 1. Selecting Investigator and monitors *21 CFR 312.53 (Sponsor*): Select investigators qualified by training and experience as appropriate experts to investigate the drug. Select monitors qualified by training and experience to monitor the progress of the investigation.  N/A | | |
| Yes  No | Form FDA-1572 for each site | |
| Yes  No | Curriculum Vitae for each principal investigator showing the experience that qualifies the investigator for the specific trial | |
| Yes  No | Financial disclosure information for each investigator | |
| Yes  No | Protocol for each site, if they differ | |
| Yes  No | Curriculum Vitae for each monitor showing the experience that qualifies the monitor for specific trial | |
| 1. Informing Investigators *21 CFR 312.55* (Sponsor): Keep investigators informed of new observations on the drug, particularly with respect to adverse effects and safe use.  N/A | | |
| Yes  No | Documentation of communication with investigators with respect to new observations | |
| Yes  No | Documentation of communication with investigators with respect to adverse events and safety reporting | |
| Yes  No | Current Investigator Brochure, if applicable | |
| Yes  No | All pertinent correspondence between sponsor-investigator and investigators at other sites. | |
| 1. Review of ongoing investigations *21 CFR 312.56* (Sponsor): Monitor the progress of all investigations being conducted under the IND. Assure the compliance of all investigators with the signed agreement Form FDA-1572, the general investigational plan, and the IND regulations.  N/A | | |
| Yes  No | Monitor reports and monitoring log for the investigation | |
| Yes  No | All correspondence with monitors | |
| Yes  No | Discontinue the participation of non-complying investigators, secure, unused drug, and notify the FDA. | |
| 1. Investigator Reports *21 CFR 312.64* (Investigator): Discontinue the participation of non-complying investigators, secure unused drug, and notify the FDA. Review and evaluate the evidence relating to the safety and effectiveness of the drug. Submit reports regarding safety to the FDA, Submit annual reports to the FDA on the progress of the investigation.  N/A | | |
| Yes  No | Documentation of a safety monitoring plan | |
| Yes  No | Documentation of a data monitoring plan | |
| Yes  No | Documentation of review of safety and data as outlined in the data safety monitoring plan | |
| Yes  No | Form FDA-1571 and accompanying documentation for each annual report | |

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| When investigations are determined to present an unreasonable and significant risk to subjects, discontinue investigations within 5 working days of the determination, and notify the FDA, all IRBs, and all investigators, assure the disposition of all stocks of the drug outstanding as required by 21 CFR 312.59, and furnish the FDA with a full report of these actions. | |
| 1. IND Safety Reporting/Review of Safety Information *21 CFR 312.32* (Investigator/Sponsor): The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies[[2]](#endnote-2), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States*.*[[3]](#endnote-3) N/A | |
| Yes  No | Notify FDA and all participating investigators in an IND safety report of potential serious risk[[4]](#endnote-4) as soon as possible (no later than 15 calendar days) after the sponsor determines that the information qualifies for reporting: Adverse event[[5]](#endnote-5), Life-threatening adverse event[[6]](#endnote-6), serious adverse event[[7]](#endnote-7), suspected adverse reaction[[8]](#endnote-8), unexpected adverse event[[9]](#endnote-9), serious and unexpected adverse event[[10]](#endnote-10), a single occurrence of an event that is uncommon[[11]](#endnote-11), one or more occurrence of an event[[12]](#endnote-12), an aggregate analysis of specific events[[13]](#endnote-13), unexpected fatal or life-threatening suspected adverse reaction reports[[14]](#endnote-14), reporting format or frequency[[15]](#endnote-15), investigations of marketed drugs[[16]](#endnote-16), reporting study endpoints[[17]](#endnote-17). |
| Yes  No | Identify all IND Safety Reports previously submitted to FDA concerning a similar suspected adverse reaction |
| Yes  No | Analyze the significance of the suspected adverse reaction |
| Yes  No | Analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. |
| Yes  No | IND safety report in narrative format, FDA Form 3500A or in an electronic format that FDA can process, review, and archive for safety reporting. |
| Yes  No | Each notification to FDA must bear prominent identification of its contents, “IND Safety Report,” and must be transmitted to the review division in the Center for Drug Evaluation and Research that has responsibility for review of the IND. Upon request from the FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. |
| Yes  No | Promptly investigate all safety information it receives. |
| Yes  No | Relevant follow up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., “Follow up IND Safety Report.” |
| 1. Record Keeping and Record Retention *21 CFR 312.57* (Sponsor)*:* Maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug (to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment)*.*  N/A | |
| Yes  No | Drug Accountability Log (if received from outside)- receipt date, quantity, lot#, return/disposition, method of disposal |
| Yes  No | Drug Accountability Log ( if shipped by sponsor-investigator to other sites)-date, destination, who shipped, quantity, lot#, return/disposition and method of disposal |
| 1. Investigator record keeping and record retention *21 CFR 312.62* (Investigator): Maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.  N/A | |
| Yes  No | Enrollment/Randomization log |
| Yes  No | Drug Dispensing Record (date, lot#, quantity, ID of subject, ID of person dispensing, and record of return/disposition |
| 1. Investigator Reports *21 CFR 312.64* (Investigator): Prepare and maintain adequate and accurate case histories that record all observations and other pertinent data to the investigation (including documentation that informed consent was obtained prior to participation in the study) on each individual administered the investigational drug or employed as a control in the investigation. Maintain complete and accurate records showing any financial interests showing any financial interest of the investigators as related to the investigational study. Retain the records and reports for 2 years after a marketing application is approved for the drug, for 2 years after the shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified.  N/A | |
| Yes  No | Source data |
| Yes  No | Case report forms |
| Yes  No | Subject eligibility documented |
| Yes  No | Concomitant medications recorded |
| Yes  No | Original signed consent forms |
| Yes  No | Documentation that informed consent was obtained prior to study procedures |
| Yes  No | Documentation that subject was given a copy of signed and dated consent form |
| Yes  No | Date/signature of staff recording data onto forms |
| Yes  No | Staff signature log |
| Yes  No | Financial disclosure |
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| 1. Controlled Substance/Handling of controlled substance Investigator Reports *21 CFR 312.69* (Investigator): If the investigational drug is listed as a controlled substance, assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance to into illegal channels of distribution.  N/A | |
| Yes  No | Temperature monitoring log |
| Yes  No | Humidity monitoring log |
| 1. Disposition of unused supply of investigational drug *21 CFR 312.59* (Sponsor):Assure the return or alternative disposition of all unused supplies of the investigational drug from all investigators. Maintain written records of any disposition of the drug in accordance with 21 CFR 312.5*7*  N/A | |
| Yes  No | Drug Accountability Log |
| Yes  No | Drug Dispensing Log |
| 1. Control of the investigation drug *21 CFR 312.61* (Investigator): Administer the drug only to subjects under the personal supervision of the investigator or a sub-investigator responsible to the investigator.  N/A | |
| Yes  No | Delegation log |
| 1. Assurance of IRB review *21 CFR 312.66* (Investigator):Assure that an IRB will be responsible for the initial and continuing review and approval of the proposed clinical study. Assure prompt reporting to the IRB of all changes in the research activity and all unanticipated problems involving risk to human subjects. Assure that no changes are made in the research without IRB approval, except where necessary to eliminate apparent immediate to human subjects. N/A | |
| Yes  No | Initial review |
| Yes  No | Clinical protocol |
| Yes  No | Informed consent form |
| Yes  No | Recruitment |
| Yes  No | Continuing review |
| Yes  No | Amendments |
| Yes  No | Reports of unanticipated problems |
| Yes  No | Protocol deviations involving risk |
| Yes  No | Current investigators brochure/device manual |
| Yes  No | Other IRB correspondence |
| Yes  No  N/A | From each site in a multi-site study, copies of the IRB approval documents (initial and continuing) |

1. A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation (21 CFR 312.33). [↑](#endnote-ref-1)
2. ***Findings from animal or in vitro testing*** – The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation. [↑](#endnote-ref-2)
3. ***Findings from other studies*** – The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation. [↑](#endnote-ref-3)
4. ***Increased rate of occurrence of serious suspected adverse reactions*** – The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. [↑](#endnote-ref-4)
5. ***Adverse event*** – any untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related. [↑](#endnote-ref-5)
6. ***Life-threatening adverse event or life-threatening suspected adverse reaction*** – is considered “life-threatening”, if in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. [↑](#endnote-ref-6)
7. ***Serious adverse event or serious suspected adverse reaction*** – An adverse event or suspected adverse reaction is considered “serious”, if in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. [↑](#endnote-ref-7)
8. ***Suspected adverse reaction*** – any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. [↑](#endnote-ref-8)
9. ***Unexpected adverse event*** – is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. [↑](#endnote-ref-9)
10. ***Serious and unexpected suspected adverse reaction***– The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as: [↑](#endnote-ref-10)
11. ***A single occurrence*** of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); [↑](#endnote-ref-11)
12. ***One or more occurrences*** of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); [↑](#endnote-ref-12)
13. ***An aggregate analysis of specific events*** observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. [↑](#endnote-ref-13)
14. ***Unexpected fatal or life-threatening suspected adverse reaction*** *reports* – The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. [↑](#endnote-ref-14)
15. ***Reporting format or frequency*** – FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND. [↑](#endnote-ref-15)
16. ***Investigations of marketed drugs*** – A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80 of this chapter). [↑](#endnote-ref-16)
17. ***Reporting study endpoints*** - must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality). [↑](#endnote-ref-17)