Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) Activity

Answer Key

Table	Scenario Description	Phase	Review Comments	Questions/Discussion Items
1	Version 1.0 of a protocol receives final signoff from the DAIDS Regulatory Affairs Branch (RAB) and is submitted to Network Operations Centers for distribution to sites. The Network Operations Center distributes Version 1.0 to your site.	Pre-Study		
1	IRB submissions have been made on time, but the IRB is extremely slow to respond, and the site can't move forward with the study without the IRB approval.	Ongoing visits		
1	A participant in a study presents with liver failure due to diffuse hepatic necrosis without any underlying liver disease. Protocol-related documents and other relevant sources of information only refer to elevated hepatic enzymes or hepatitis as potential adverse events related to the procedures involved in the research.	Ongoing visits		

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1	A participant enrolled in a phase III, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that the there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all participants enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency.	Ongoing visits	Adverse Event (AE) is within expected frequency. Not an UAP.	
1	A subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol due to a processing error by a pharmacy technician. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation.	Ongoing visits		

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1	A protocol is amended to add urine collection to an approved study.	Ongoing visits	Addition of new study procedure likely to result in Letter of Amendment (LoA).	
1	Your site investigator receives an off-site AE report that does not result in a change to the study risk and does not require modifications to study documents.	Ongoing visits		What to do with off-site (external) AE reports relating to the study drug from other trials using the same study agent.
1	A female participant exposed to study agent F due to her involvement in a clinical trial gives birth to a child. Clinicians note a major cardiac defect at birth along with several clinically insignificant physical findings. The congenital anomaly is determined to be unexpected and there is reasonable possibility of relation to the study agent.	Ongoing visits	Congenital anomaly SAE elevated to SUSAR due to being unexpected and related.	Reporting to pregnancy exposure registries (ex. PROMISE study). See protocol requirements for reporting pregnancy registry data to IRBs
1	Per updates in federal regulations, informed consent forms will require additional elements related to use of de-identified information, use of biospecimens, and potential for commercial profit and return of clinically relevant results. Your research site elects to update the informed consent form to reflect these new elements for ongoing studies, ahead of when the policy becomes effective for all new studies.	Ongoing visits		Revised Common Rule.What types of changes will result in having to reconsent participants?

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1	A research participant files a complaint to clinic research staff regarding a clinic nurse performing a procedure at a recent study visit in which the nurse was not qualified to perform.	Ongoing visits	If the complaint remains unresolved it must be reported to the IRB.	
2	A study is prematurely terminated based on sponsor decision.	End of Study		
2	New protocol version 3.0 is released for a phase 2b study to evaluate the safety and efficacy of VRC01 in reducing HIV-1 acquisition.	Ongoing visits		
2	A participant presents with Hodgkin's disease (HD) without predisposing risk factors for HD. Protocol-related documents and other relevant sources of information only refer to acute myelogenous leukemia as a potential adverse event.	Ongoing visits	Report	
2	A participant in a clinical trial dies as a result of a motor vehicle crash. The investigators conclude that the participant's death was unlikely to be related to the research interventions.	Ongoing visits Summarize AEs at Continuing Review	Not related to research intervention.	What about other sudden, accidental, or traumatic deaths (ex. suicide, death unwitnessed at home) possibly related to study intervention?

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2	A HIV/AIDS clinical trials network elects to reallocate enrollment slots among clinical research sites for Protocol X. Your site, originally approved to enroll 100 participants, is now granted 50 additional slots for a maximum of 150 participants.	Enrollment	Report	Rules around what sites must report to the IRB regarding enrollment numbers (ex. when enrollment is below, at, or above the # of allocated slots; when your # of slots are reduced/increased)
2	A new study suggests an increased risk of birth defects in babies born to women taking dolutegravir at time of conception. The protocol study team for an in-progress phase I/II multicenter open label pharmacokinetic safety, tolerability, and antiviral activity of dolutegravir study in HIV-1 infected infants, children, and adolescents releases an amendment that includes protocol updates to ensure documented contraception use for female participants of child bearing potential.	Ongoing visits		

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2	A clinical research site located at a local HIV/AIDS clinic uses a text notification system for appointment reminders. Research staff send a text reminder to a participant regarding their upcoming visit at the clinic, however this participant did not previously consent to receiving text notifications. The participant is inadvertently outed when a work colleague sees the notification appear on their phone.	Ongoing visits	Inadvertent disclosure of patient health information and possibly HIV status.	
2	A new version of the Investigator Brochure for an enhanced anti-HIV-1 broadly neutralizing antibody becomes available through the electronic system for Investigator Brochure distribution.	Ongoing visits		
2	A clinical research site receives a call from the FDA/EMA to schedule an inspection.	Ongoing visits		
2	A participant is hospitalized for grade 4 pancreatitis that is unexpected and there is a reasonable possibility that the AE is related to participation in the research.	Ongoing visits		
3	Version 1.0 of a protocol is released and will be conducted in both the U.S. and South Africa. IRBs at U.S. sites deem the study to be of minimal risk, whereas your IRB in South Africa determines the protocol to be greater than minimal risk.	Pre-Study	Revised Common rule and FDA/EMA regulations still apply. Expedited review depends on your IRB's determination of study risk.	Local IRB rules regarding expedited review Revised Common Rule changes affecting minimal risk studies

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3	Recent updates to U.S. federal policy have resulted in changes that require a "Key Element" summary to be added to the beginning of all informed consent forms, to be in effect for all new studies next year. Your site elects to implement the change now for all current, ongoing protocols.	Ongoing visits		Revised Common Rule. What types of changes will result in having to reconsent participants?
3	The fifth subject enrolled in a phase II, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent.	Ongoing visits	Report	

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3	An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting.	Pre-Study	Not an unanticipated problem because the death of the participant is not related to participation in the research but is most likely related to the infant's underlying medical condition.	
3	An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors. Data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.	Ongoing visit		
3	A participant engaged in a vaccine study becomes incarcerated during the conduct of the study. The protocol was not approved to enroll prisoners.	Ongoing visits	IRB approval needed for continuation of prisoner's participation in the research.	
3	A clinical research site is notified of an institutional data breach that resulted in the release of some medical patient's names, medical record numbers, and other information on the internet.	Ongoing visits	report	

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3	A site maintains a stock of infrequently used topical medications for use in a clinical trial. During a study visit, site staff go to retrieve the medication for a participant but see that the stock is now expired, and no unexpired drug is available.	Ongoing visits	Loss of study drug.	
3	A dear participant letter is being used in this study and needs to be approved by the IRB.	Enrollment		
3	A multi-arm clinical trial evaluating two antiretroviral (ARV)-based approaches for preventing sexual transmission of HIV in women (a vaginal gel or daily use of one of two different ARV tablets) elects to drop one of the oral tablets from the study due to failure to demonstrate efficacy.	Ongoing visits		
4	A study is suspended based on sponsor decision.	End of Study		
4	The Data and Safety Monitoring Board (DSMB) for a phase II multi-center, randomized clinical trial convened for an annual review of accumulated safety and enrollment data. A summary report is written at the conclusion of the meeting and provided to the investigator.	Ongoing Visits		
4	A participant involved in a two-arm comparison study of drug A versus drug B receives the wrong study agent. The participant is monitored for adverse effects and does not experience any.	Ongoing visits	Receiving the wrong study agent is always an unanticipated problem even if there is no AE.	

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4	A female participant exposed to study agent C due to her involvement in a phase I clinical trial gives birth to a child. Clinicians note a major cardiac defect at birth along with several clinically insignificant physical findings. The congenital anomaly is deemed not related to the study agent and is reported to DAIDS within 3 reporting days.	Ongoing visits	Not an unanticipated problem due to no relation to participation in the research (not related to study agent).	Reporting to pregnancy exposure registries (ex. PROMISE study). See protocol requirements for reporting pregnancy registry data to IRBs
4	17 research sites are participating in a study comparing an investigational agent to standard therapy in subjects ages 18-25. Of those subjects receiving the investigational drug, an average of 35% of subjects across the 17 sites experience deep vein thrombosis.	Ongoing visits	Report	Responsibility of site vs. sponsor to report aggregate adverse event data to IRB. How do sites get notified of aggregate safety data? DSMB, SMC...
4	The first implementation version of a trial protocol is distributed to your site.	Pre-Study		
4	A pediatric research protocol is amended to add allergy skin testing.	Ongoing visits	Addition of new study procedure likely to result in LoA.	What types of changes will result in having to reconsent participants?

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4	A participant involved in a phase II study reports the new onset of a migraine which lasted two days and caused the participant to remain bedridden and miss work.	Ongoing visits	Severe intensity AE, but not serious, life threatening, and did not result in hospitalization or disability.	
4	A participant involved in a double-blind study experiences a medical emergency. The investigator deems unblinding of the participant necessary, calls the site pharmacist to access unblinding codes, and identifies the investigational product assignment of the individual participant.	Ongoing visits	Report	Reminder about network SOPs regarding emergency unblinding.
4	Your site receives a clarification memo for a study that does not result in a change to the protocol informed consent document.	Ongoing visits		Reporting requirements for clarification memos vs. LoA vs. new protocol versions