2022 Ethics Case and Facilitator Guide - Use of Human Biospecimens and Informed Consent

Overview

Please remember to distribute the case in advance of the training to allow participants time to review and digest the material.

This year's case is a bit different from previous year's cases because it includes some technical material pertaining to the regulation of research with human subjects. Since this material may be unfamiliar to some staff (audience members?), it may be appropriate to include some didactic content as part of the session. Nevertheless, as in previous years, a fair, balanced, open, and insightful discussion should be the main goal, not lecturing.

The case deals with the following topics:

1. Including underrepresented groups in research.
2. Non-compliance with human subjects regulations; what it is (in this case), why it happens, how to prevent it, and what to do about it.
3. Consent for research involving secondary use of human biospecimens or data.
4. Dynamics and leadership of the research group, especially openness to discussion about scientific, regulatory and ethical issues.
5. Disposition (e.g., publication, use) of data that resulted from non-compliance or unethical conduct.

Probably the most controversial topic is #5, because important moral or ethical values are in conflict (i.e., publishing research with important public health impacts and not wasting time and resources vs. ensuring compliance with regulations and respecting the rights of research participants).

The case is long and could easily take two hours to discuss all of it, so proper pacing is essential. It is very important to get to Part IV Question 12.

To make the case interesting, it is important that the audience empathize with researchers and view them as intelligent, well-meaning people who made a mistake. The audience should realize that something like this could happen to them. This gives the case practicality and urgency.

Key Take Home Points

1. Before sharing human biospecimens or private data, it is essential to check with the IRB-approved informed consent document to determine whether and exactly what sharing is permitted. If participants have opted not to allow their biospecimens or private data to be shared with other researchers outside of the original study team, their wishes must be respected.

2. **Secondary research** on human private data or biospecimens is research that **is not part of the original IRB-approved protocol**, such as investigation of a new question or hypothesis, or a new analysis of the data.
3. **Secondary research involving the use of identifiable**, private human data or identifiable human biospecimens **must be approved by the IRB**.
4. Human data or biospecimens are considered **identifiable** if they include personal identifiers (such as name or medical record number), or they are coded and a member of the research team has access to the key needed to decipher the code.
5. Secondary research on **non-identifiable private**, human data or biospecimens does not require IRB approval, provided that it is consistent with the IRB-approved protocol and consent form.
6. **It is always a good idea to consult with the IRB if you have any questions about sharing human biospecimens or data or conducting research on private human data or biospecimens. Stress this point! If attendees do not remember anything from this training, they must remember that it is always a good idea to contact the IRB if they have questions about sharing human biospecimens or data or conducting research on private human data or biospecimens.**

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Part I: Inclusion of Underrepresented Populations in Clinical Trials, Statistics, Demographics

Dr. Maxwell is a cell biologist and a Senior Investigator at the NIH who has been collaborating with Dr. Liu, an oncologist and Clinical Investigator at the NIH. Maxwell and Liu have published numerous articles in high-impact journals on using RNA-interference (RNAi) to treat liver cancer. The RNAi treatment works by blocking expression of a genetic variant that plays a key role in liver cancer cell proliferation. After successfully treating liver cancer in laboratory mice and completing a Phase I trial which showed the treatment was well tolerated, they began a Phase II trial. However, few subjects receiving the treatment had stable tumor volume for 12 months, the study's efficacy measure. Interestingly, the treatment was more effective in African American/Black males than in other racial, ethnic, or gender groups, although the proportion of African American/Black males with stable tumor volume compared to other groups was not statistically significant ($p = 0.07$). The trial recruited a diverse population of subjects but was insufficiently powered to establish efficacy in isolated demographic groups.

1. Is $p = 0.07$ considered to be a statistically significant difference between demographic groups? How should the investigators address this finding?
   Although $p \leq 0.05$ or less is commonly used as an indicator of statistical significance, p values > 0.05 might still provide investigators with important information, depending on the study design and sample and effect size. Although the treatment was not effective when the entire study population was considered, subgroup analysis showed that the treatment resulted in a trend ($p= 0.07$) toward efficacy in the African American male subgroup. The investigators should discuss the effect size seen in African American males with a statistician and design a future study with enough subjects in that group to determine if treatment is efficacious in that group at a p-value ≤0.05.
2. How should the investigators have designed their Phase II trial if the goal had been to distinguish between treatment effects in different demographic groups? Would this change in strategy have created any issues for completing their study?
   This was only a Phase II study, so the main goal was probably just to test for efficacy, not to analyze treatment effects in different groups. If the goal of the study had been to distinguish between treatment effects in different demographic groups, the investigators should have tried to recruit enough participants to achieve the required statistical power, based on estimates of effect size. However, estimates of effect size can be erroneous, since they may be based on limited or inconsistent data. Also, increasing the number of participants would make it more difficult to conduct the study, due to increased costs and additional time needed to meet recruitment goals. A larger, Phase III study could seek to gather additional data on efficacy and distinguish between effects in different groups. The NIH has a policy on inclusion of women and minorities in clinical research that applies here.

https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm. According to the policy, women and members of minority groups must be included in NIH funded clinical research unless there is a clear and compelling rationale for exclusion. Research plans and proposal must include a description of the population and measures that will be taken for recruiting women and minorities. When a Phase III clinical trial is proposed, evidence must be reviewed to determine whether racial/ethnic or gender differences are expected. If differences are expected, the research plan or proposal must include plans to conduct analyses to detect significant differences in treatment effects. Studies must be appropriately statistically powered. If no differences are expected, investigators are encouraged to include plans to conduct analyses to detect differences, but such plans are not required. If prior evidence neither supports nor negates differences, the study should include sufficient and appropriate data on race/ethnicity and gender, so that analyses can be conducted, but these studies do not need to be statistically powered to detect an effect. It is also important to note that the NIH is committed to research that improves the health equity and well-being of vulnerable populations, including "racial and ethnic minority groups as defined by the Office of Management and Budget, along with persons of less privileged socioeconomic status, underserved rural residents, sexual and gender minorities, and persons with poor health due to social disadvantage." https://www.nimhd.nih.gov/programs/intramural/ Investigating demographic differences pertaining to the effects of treatment in clinical trials helps to promote the NIH's commitment to research and helps vulnerable populations.

3. What are some strategies for including underrepresented populations in research? **Strategies could include special efforts to recruit and reach out to underrepresented populations and collaborating with research organizations, researchers, health care clinics, pharmacies, civic organizations, or churches that serve underrepresented populations.**

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Part II: Scientific Disagreements

Following the disappointing Phase II trial, the investigators try to understand, at a cellular level, why the treatment works in some participants but not others. They decide to try to model their RNAi treatment in mouse organoids (self-organized tissue constructs derived from stem cells) to elucidate molecular, genetic, and epigenetic mechanisms and interactions. Maxwell invites Dr. Mehta, a Visiting Fellow, to join the team and puts Mehta in charge of the animal organoid experiments. Mehta and Maxwell discover a genetic variant that interferes with the RNAi treatment in mouse liver tumor organoids. They also discover that it is possible to use a different RNAi treatment to block expression of the variant.

At a lab meeting, Maxwell announces plans to test this two-pronged RNAi approach to liver cancer in their mouse model. Mehta asks whether additional analysis of the organoid data needs to be done before proceeding further, but Maxwell rejects this idea Later that day, Maxwell asks Mehta for an impromptu meeting in which Maxwell says "Dr. Mehta, I have a great deal of respect for your judgment and expertise but if you disagree with me about a scientific issue, we should discuss it in private and not in front of the group."

4. How should disagreements about scientific issues be handled? What are the advantages and disadvantages of discussing them with the whole research team?
   It depends on the issue. If the issue concerns the entire research team, it should be discussed openly with the team, so that everyone understands the issue and can contribute to the discussion. Bringing the issue to the entire team can improve the quality of decision-making by allowing team members to share arguments, perspectives, and information that might not have been considered if the issue were handled privately. Also, when a decision is reached, members of the research team may appreciate being included in the decision. They may also feel that they have some ownership of the decision and that it has been reached fairly, both of which are good for morale. Additionally, discussion of scientific issues can be a good opportunity for mentoring, i.e., to show trainees how issues arise, how they are discussed, and how they are resolved. If the issue is a private or personal matter (e.g. such as a work performance issue), it should not be discussed with the entire research team. In this particular example, Maxwell should not have discouraged Mehta for bringing the issue about the need for additional analysis and model development to the research team because it did concern all members of the team. By doing this, Maxwell also discouraged Mehta from bringing up other issues that might be important. Free, open, and candid dialogue and discussion should be encouraged, not discouraged. Maxwell is running the team more like a dictatorship than a democracy.

Part III: Research with Human Biospecimens, Sharing Biospecimens, Consent

After a year, the team has completed the animal experiments, which show that the new, two-pronged RNAi treatment is 95% effective at halting tumor growth in their mouse model. Maxwell and Mehta discuss these findings in Maxwell's office. Maxwell believes the experiments should be replicated as soon as possible in human organoids, but Mehta thinks they need to do some additional work with animals before proceeding further. Maxwell dismisses this concern and says that the lab already has some cancer stem cells in storage from the Phase II collaboration with Liu that they can use to develop human, liver tumor organoids. Later, Maxwell emails Liu about this project, who is excited about the idea.

At a lab meeting the following day, Maxwell informs the group about the plans for the human tumor organoid experiments and puts Mehta in charge of the project. Maxwell also says they will send aliquots from the human organoids to Dr. Kennedy, who runs an NIH Genomics Core Facility and will test for the variant that blocks the original RNAi treatment. Kennedy will also perform gene expression assays on the aliquots. Mehta, who recently attended an NIH workshop for trainees on the responsible conduct of research, asks if they will need Institutional Review Board (IRB) approval before they proceed. Maxwell quickly and forcefully responds that the project will not be considered human subjects research because the cells are marked with a code and only Liu has access to the key needed to decipher the code, but Liu is not part of the research team. Mehta feels that Maxwell was irritated by the question and does not pursue the matter further.

5. Do the researchers need to ask the IRB for permission to send human biospecimens to Dr. Kennedy or any other collaborators?
   No, but the researchers need to comply with the language in the consent form. Most consent forms give participants the option of permitting or not permitting sharing. Researchers must keep track of this information and honor the participants' wishes. If participants consented to sharing of samples for this purpose (e.g., cancer research) or for general purposes, they may share the samples. <u>If the participants have said they do not want their samples shared, the researchers must honor their wishes.</u> If the consent form was silent on the topic of sharing (which may be the case with older forms), they may share the samples, provided that sharing does not conflict with other language in the consent form. Although they do not need IRB's permission to share samples, they should consult with the IRB if they have questions about sharing. If they plan to send samples to external collaborators (i.e., outside NIH), a material transfer agreement (MTA) will also need to be signed, and as part of this process the investigator will have to sign a form attesting to the fact that the previous consent form is consistent with the planned sharing and research. Note: Some ICs require the use of MTAs for sending samples within the NIH.

6. Does it matter what the consent form says about future use and sharing of human biospecimens?
   Yes, it does matter. If the consent form included language about sharing for future research or was silent on the topic, they can be shared. If the participants have opted out of sharing as part of the consent or there is other language which restricts sharing, then the biospecimens may not be shared. If the investigators have questions about the consent language, they should contact the IRB.

7. Should Mehta have said something to Maxwell about the human subjects issue before the lab meeting? What difference might that have made?
   Probably, because Maxwell might have been more receptive to the concern if it were communicated in private. Since they have already had a disagreement about bringing issues to the group, bringing it up at the lab meeting may have irritated Maxwell further and made Maxwell less receptive. However, this is really Maxwell's problem. Mehta should not have to debate as to whether to bring this issue up in private. Maxwell should be open to feedback and critical discussion. By discouraging open discussion, Maxwell is running the risk that a key regulatory/ethical issue will be overlooked.
8. Does secondary research with human biospecimens require IRB approval if the biospecimens are coded and none of the members of the research team working with biospecimens have the key to the code?
   Secondary research on human private data or biospecimens is research that is not part of the original IRB-approved protocol, such as investigation of a new question or hypothesis, or a new analysis of the data. Secondary research involving the use of identifiable, private human data or identifiable human biospecimens must be approved by the IRB. Human data or biospecimens are considered identifiable if they include personal identifiers (such as name or medical record number), or they are coded and a member of the research team has access to the key needed to decipher the code. Secondary research on non-identifiable private, human data or biospecimens does not require IRB approval, provided that it is consistent with the IRB-approved protocol and consent form. It is always a good idea to consult with the IRB if you have any questions about sharing human biospecimens or data or conducting research on private human data or biospecimens. Researchers may also request the IRB to make an official determination that their research is "not human subjects research." While this is not required, it can be useful when submitting articles to journals, because reviewers and editors may request information about human subject approvals. Requests for determinations can be submitted through IRIS: https://irb.nih.gov/ For additional information and guidance, review the presentation by Julie Eiserman and Jonathan Green.
9. If someone has questions about whether a study requires IRB approval, who should they contact for advice?

Call the IRBO at 301-402-3713 , contact your IC's IRB Team Lead, or send email to IRB@od.nih.gov. Contact Julie Eiserman julie.eiserman@nih.gov for questions about sharing and secondary use of biological samples or data.

10. Generally, who is responsible for ensuring the regulatory issues, including human and animal subjects issues, are properly addressed?
    Although this responsibility falls most heavily on the team leader (or principal investigator), all members of the research team are responsible for ensuring that regulatory issues are properly addressed. For this reason, it is important to be able to discuss regulatory concerns openly among team members. Note: NIH researchers who direct core facilities (i.e., Dr. Kennedy in this case) may wonder whether they have any responsibilities regarding compliance with regulations when they receive human biospecimens. The NIH IRB's policy is that these responsibilities fall on the principal investigator sending the biospecimens for analysis. That being said, it would be a good idea for the core facility director to discuss regulatory issues with the sender of the biospecimens if they have any questions or concerns.

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Part IV: Human Subjects Research and IRB Review

After six months, the researchers have enough data to show that the two-pronged RNAi approach is highly effective at stopping liver tumor growth in human organoids. During a lab meeting, Maxwell discusses their exciting results and the possibility of initiating another clinical trial in collaboration with Liu. Maxwell asks Mehta to assemble individual, participant-level data from their research for Liu. Maxwell believes the data are compelling enough for Liu to revisit the clinical data from the Phase II study so that Liu can determine whether participants without the variant of interest responded better to the original RNAi treatment than those with it. Mehta is still concerned about the IRB issue, since they are now planning to share individual, participant-level coded data with Liu. Mehta is hesitant to discuss these regulatory/ethical issues with Maxwell, given the tensions in their relationship.

11. What should Mehta do at this point? **Mehta should bring this issue up with Maxwell and Liu and contact the IRB office if the issue has not been resolved satisfactorily. There are other offices that Mehta can also contact for help and support, such as the Clinical Director, the Training Director, and the Ombudsman.**

12. Is IRB approval needed to share the coded participant-level data with Liu? Is it needed for Liu to perform this new analysis of the clinical data from the Phase II study? **IRB approval is needed if Liu will be receiving individual-level results because Liu has the key to the code and could identify these participants. IRB approval is also required for Liu to perform this new analysis because, again, Liu has access to personal identifiers. Liu's research would be considered "human subjects research" because Liu will be doing a new analysis on identifiable human biospecimens, and this research is not currently addressed in any IRB-approved protocol. It would be a new study.**

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Part V: Manuscript Clearance/Submission, IRB, and Non-Compliance

Mehta deliberates about what to do but doesn't want to further jeopardize the relationship with Maxwell and ultimately decides to say nothing. Liu receives the individualized data and begins the analysis using the prior Phase II data. Liu finds that participants in their Phase II study without the variant of interest were five times more likely to respond well to the original RNAi therapy than participants with the variant. Maxwell drafts a paper to submit to the *Journal of Breakthrough Medical Results*. After the paper makes it through the NIH manuscript clearance process—Maxwell checked the "no" boxes when asked whether the manuscript was based on a clinical study protocol or exemption—the authors submit it to the journal. After 6 weeks, journal accepts the paper with minor revisions. One of the reviewers asks whether they had IRB approval for this study. Liu reads the comment and is floored because Liu realizes that IRB approval was needed but was not obtained. Maxwell realizes they had incorrectly completed the manuscript clearance form. Liu feels angry and embarrassed, wondering if excitement about moving forward with this project led to neglect of IRB issues. Liu meets with Maxwell to discuss their problems.

13. How should they proceed from here? Should they contact the IRB?
Yes, they should contact the IRB immediately. They should also contact the editors of the journal.
14. Should the researchers withdraw the paper? **Yes, given the regulatory and ethical issues with it. The journal and the IRB may require it to be withdrawn in any case.**
15. Should the reviewer for NIH publication clearance have checked to see if the authors checked the wrong box?
Possibly, but the NIH publication clearance system is based on trust. Researchers submit their publications to the system and provide information to reviewers, often by checking boxes. Reviewers expect that submissions will be truthful and accurate and do not normally verify information that is submitted. It is worth noting, however, that if the reviewer read the paper carefully, they would realize that it involved human biospecimens and they would look for information about IRB review in the methods section of the paper. A careful reading of the paper might lead them to ask questions about whether boxes were checked correctly and whether IRB review was needed.

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Part VI: Research Non-Compliance, Corrective Actions, and Publication

Liu contacts the NIH IRB about what happened. The Executive IRB Chair, Dr. Anderson, tells Liu to stop all research on this project and submit a Reportable Event Form (a form for reporting non-compliance, protocol deviations, and other problems with research). Anderson reviews the Reportable Event Form and the protocol and consent forms from the Phase II study and notices that the consent form includes the following language:

"Check yes or no for each statement:

I agree to allow my biological specimens and data to be stored and used for other research studies [Yes__No__]

I agree to allow my biological specimens and data to be shared with other researchers [Yes__No__]

Anderson asks Liu if they kept records of what the subjects consented to and honored their requests. Liu contacts the study coordinator who reports the following breakdown:

I agree to allow my biological specimens and data to be stored and used for other research studies [Yes: 75, No: 15, No Answer: 10]

I agree to allow my biological specimens and data to be shared with other researchers [Yes: 75, No: 15, No Answer: 10]

Anderson realizes that the non-compliance is potentially more serious than it seemed to be initially because 15% of the subjects did not want their biospecimens or data used in other studies and 15% did not want their biospecimens to be shared with other researchers. Anderson discusses this issue with Liu and learns that biospecimens and data from all of the participants were included in the research and biospecimens from all of the participants were shared with Kennedy. The IRB reviews the reportable event at its next meeting and decides that this is serious non-compliance. The IRB is required to report this non-compliance and corrective actions to the HHS Office of Human Research Protections, which oversees NIH-funded research.

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The IRB is trying to decide what type of corrective actions need to occur.

16. Which of the following corrective actions should be taken (if any)?

    a. Contact the participants whose consent was violated and tell them what happened and what is being done about it and apologize;
    Yes, contacting the participants helps to right the wrong and embodies the virtues of transparency and honesty. It is unclear whether all the participants should be contacted or only those whose consent was violated. If consent was not violated, contacting them might not serve a useful purpose and may create confusion and distrust. However, it may be wise to contact all the participants because they might learn about what happened (for example, from a news report or a friend in the study) and they might become suspicious if they were not contacted.
    b. Require additional training for Liu and Maxwell and their research groups on human subject protections;
    Of course.
    c. Require more training throughout the NIH on IRB approval for secondary uses of biospecimens and data;
    Probably, it depends on whether this is a unique case or is part of a larger pattern of misunderstanding of or lack of concern for regulations. If the latter, training throughout the NIH is warranted.
    d. Prohibit Liu and/or Maxwell from doing research with human subjects for a period of time, such as a year or more;
    This is a harsh punishment but may be appropriate, depending on whether there are aggravating circumstances, such as bad intent, lack of cooperation, and a history of non-compliance. If the IRB determines that this was an honest mistake and that there was no history of non-compliance, and Liu and Maxwell cooperate fully with IRB during its investigation and adjudication, then a lesser punishment, such as supervision of research and a probationary period, may be appropriate. Note: the IRB does not have the authority to stop investigators from doing research. It can approve, disapprove, suspend, or terminate protocols, but not investigators. The IRB would need to work with the Clinical Director, Scientific Director, and other IC or NIH leaders to implement and enforce sanctions.
    e. Require the paper to be withdrawn; **This is a good idea, given all the issues with the paper.**
    f. Require that all of the human data be destroyed. **This is a difficult issue because there are conflicting moral/ethical values at stake: publishing data with potential significant impact on public health and not wasting human and financial resources vs. promoting full compliance with regulations and respecting the rights of human participants. On the one hand, the**

investigators have made an important discovery that could have significant implications for the treatment of liver cancer, or even cancer more generally. Also, the investigators have invested considerable time and government money in this project. One of them, Mehta is a postdoc who can ill-afford to lose out on the ability to publish this work. Moreover, some of the human subjects who consented to having their biospecimens used in research studies would probably be upset to find out that their biospecimens helped to make an important discovery but that the data was destroyed. On the other hand, this was a serious violation of the human research regulations because the research was conducted without IRB approval and consideration of consent for the new research. To promote compliance, the NIH should take measures to discourage non-compliance. Requiring the data be destroyed will send a clear message to other researchers at the NIH that serious non-compliance will not be tolerated. Moreover, in some instances the researchers violated the participants' consent, which is a serious ethical lapse, quite apart from the regulations. Honoring participants' wishes concerning the use of their biological specimens is important for respecting their autonomy, dignity, and rights.

g. Require that the human data where consent was violated be destroyed. **This is less drastic than the previous option and still sends a clear message that non-compliance will not be tolerated. It also respects that participants' decision concerning the use of their biospecimens and data. This option also leaves open the possibility that they could use this data for future research. Since the IRB cannot give post hoc approval to studies, the data would be used as "preliminary data" for a new, IRB-approved study. Of course, removing this data might invalidate or weaken the results, since it would require removal of a significant proportion of the data. To obtain more data, the investigators could consider asking the IRB for permission to contact the participants who did not check either the "yes" or "no" boxes for sharing of biospecimens/data or additional research. They could ask these participants for permission to share their samples and do additional research. Note: any plan to destroy data must be consistent with NIH rules on recordkeeping.**

17. Generally, what could have or should have been done to prevent these problems?
There should have been better communication about and awareness of human subject protection issues from the very beginning. Mehta's questions and concerns should not have been squelched. Other members of the team could've or should've spoken up. They should discuss potential human subjects issues as soon as they started planning to use human biospecimens in research.

18. Who is/was responsible for ensuring that they had appropriate IRB approvals for their research? Maxwell, Liu, other members of the lab present at group meetings, the NIH publication clearance reviewer, the reviewers and editors at the journal?

All of these people, but the most responsibility falls on Maxwell and Liu.

These notes were revised by the CSCE on 9/27/2022

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[Link to Survey on next page]

Please take the survey by either clicking on the link below or scanning the QR code on your hand-held device:

https://www.surveymonkey.com/r/6MRQTVW