2022 Ethics Case Study - Use of Human Biospecimens and Informed Consent

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.

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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?

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?

3. What are some strategies for including underrepresented populations in research?

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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?

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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?

6. Does it matter what the consent form says about future use and sharing of human biospecimens?

7. Should Mehta have said something to Maxwell about the human subjects issue before the lab meeting? What difference might that have made?

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?

9. If someone has questions about whether a study requires IRB approval, who should they contact for advice?

10. Generally, who is responsible for ensuring the regulatory issues, including human and animal subjects issues, are properly addressed?

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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?

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?

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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?

14. Should the researchers withdraw the paper?

15. Should the reviewer for NIH publication clearance have checked to see if the authors checked the wrong box?

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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;
    b. Require additional training for Liu and Maxwell and their research groups on human subject protections;
    c. Require more training throughout the NIH on IRB approval for secondary uses of biospecimens and data;
    d. Prohibit Liu and/or Maxwell from doing research with human subjects for a period of time, such as a year or more;
    e. Require the paper to be withdrawn;
    f. Require that all of the human data be destroyed.
    g. Require that the human data where consent was violated be destroyed.

17. Generally, what could have or should have been done to prevent these problems?

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?

[End of case study]

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