The Chordoma Foundation has anticipated common questions that patients might have about this trial, and has worked with the National Cancer Institute to create this document with answers to those questions. The answers below are from the trial investigators at the National Cancer Institute. If you have further questions, please email support@chordoma.org.

1. **How do I know if I'm eligible for this trial?**

You must meet the following criteria to be eligible:

- Have localized chordoma eligible for treatment with radiation
- Tumor must be measurable on imaging (at least 1 cm residual on MRI or CT scan)
- No evidence of metastatic disease
- Good overall health as measured by something called ECOG Performance Score. (Ask us or your doctor if you meet this criterion.)
- No major laboratory abnormalities

Our team at NIH is willing to walk you through the process if these criteria are not clear to you.

2. **What are the downsides of participating in the trial?**
   - You will have to travel to Bethesda, Maryland for all visits on the study.
   - You may have some mild side effects from the vaccine such as fever, flu-like symptoms, and injection site reactions.
   - You will not be able to participate in other clinical trials or receive any other systemic therapy while on this trial.

3. **Is there a risk in delaying radiation to get the initial doses of vaccine?**
   - The answer to this question is currently not known, but it seems very unlikely that waiting 6-8 weeks to start radiation would affect your long-term outcome. Patients often must wait for that period of time or longer to have radiation after surgery to allow for healing. Please ask your treating radiation oncologist for his/her opinion on this question before enrolling in this trial.

4. **How effective is radiation without the vaccine?**
   Radiation is the standard treatment option for patients with residual or inoperable tumor. Radiation is excellent at controlling disease growth locally, in most cases for at least 3 years, and often longer. However, eventually most chordomas in this setting will progress and it is very uncommon for tumors to shrink with radiation in this setting, and most will eventually grow. We have designed this study to see if adding the vaccine will increase the benefit of radiation both on shrinking the disease and long-term outcomes, such as length of time until tumor growth (locally or in other sites of the body).

5. **Can I participate in the trial if I have already had radiation?**
   Prior radiation does not keep you out of the trial, but you must meet all the eligibility criteria described in Question 1 above. Even if you have had prior radiation, as long as you have localized

disease and your radiation oncologist believes that he or she can treat you with the required dose of radiation or more to that site, you can participate.

6. **What can I do if I've already had radiation?**
   Ask your radiation oncologist if you can be treated again with radiation to your site of disease. If you can, you may be eligible, if you do not have metastatic disease. The NIH team will discuss with your doctor what dose they plan to use of radiation. The dose must be within certain limits, which can be discussed between your radiation oncologist and the NIH team.

7. **Is the cost of my radiation treatment covered as part of the study?**
   In most situations, the answer will be no. The NIH Clinical Center does have a radiation oncology department, but in most cases, they will not have the necessary equipment to deliver the required doses of radiation. You should plan on having your radiation with an outside doctor. As a result, the NIH cannot pay for your radiation treatments however your insurance may cover these costs. In the unlikely event that your radiation can be delivered at NIH, there would be no cost for treatment.

8. **Can I participate in the trial if I've had a complete resection?**
   No. To participate, your tumor has to be measurable on imaging. That means there must be at least 1 cm mass on MRI or CT scan prior to enrollment and radiation to be eligible for this study.
   This study is set up to evaluate the effect of the vaccine in combination with radiation. In order to evaluate that effect, we need to see some tumor so we can determine if the combination of vaccine and radiation has caused the tumor to shrink. If there is no tumor to measure, we cannot evaluate the effect.
   Therefore, if you have recently had a complete resection and have no evidence of disease, then you would not be eligible to participate. However, if you previously had a complete resection and now have a regrowth, then you could be eligible to participate.

9. **How likely is my tumor to grow if I get radiation without the vaccine?**
   Your tumor is unlikely to grow in the next 3-5 years if you get only radiation. It is also unlikely to shrink with radiation alone, and it will almost certainly grow at some point in the future. We hope the addition of vaccine will decrease the likelihood of future growth and increase the likelihood of tumor shrinkage in the near term, but we do not know if the vaccine will improve the outcome compared to radiation, alone.

10. **Aren't vaccines for preventing disease? How will a vaccine help if I already have chordoma?**
    Vaccines are for preventing disease, but this vaccine is called a “therapeutic cancer vaccine.” That means it is intended to teach the immune system something about your cancer so it can recognize and try to kill the cancer cells that make up your tumor. Once the vaccine educates the immune system (the T cells specifically), the T cells try to kill cells expressing the brachyury protein, which is present in chordoma cells almost universally.

11. **For how long am I able to continue getting the vaccine? Will this trial end at some point?**
    Currently, our plan is for the vaccine to continue indefinitely as long as your tumor has not grown. After 2 years, we may consider spacing the doses out even further (every 6 or 12 months), depending on what we have seen at that point on the study, the availability of the vaccine, and your wishes (for convenience). It is not known if vaccines for cancer need to be given in an ongoing

fashion. If they are, there is reason to believe that they can be given further apart later than they would be given initially.

12. **For how long do I have to keep coming back to NIH?**
    Initially you will come every 2 weeks (for 4 weeks before radiation and then 4 weeks after recovery from radiation), then every month for 4 doses (3 months), and then every 3 months for therapy thereafter. This treatment will continue until evidence of disease progression. If you were randomized to the placebo arm, you have the option to "cross-over" and receive the vaccine at that point.

13. **Why do I have to continue getting the vaccine?**
    We do not know for certain that you need to continue the vaccine, but we believe that continuing to boost the immune system against the target (brachyury) is likely to be beneficial. We have planned to continue boosting to increase the chances of this therapy helping to shrink the tumor or prevent it from regrowing.

14. **What happens if I decide to stop taking the vaccine?**
    You always have the option to refuse treatment on a clinical trial. Even if you stop taking the vaccine we would still like for you to return for scheduled follow-up visits so the study can generate useful information about how well this vaccine works. You are always welcome to refuse, but it will help us all understand whether this vaccine works if you continue with the study as planned.

15. **Why do some patients on the trial get a placebo?**
    In order to prove that a treatment works it must be compared to something. In this study, we have gone to great lengths to ensure that each participant is not being "undertreated." Instead, all patients will be treated with the standard therapy, radiation. Half will receive the addition of vaccine; the other half will receive a "blinded placebo." This is done so there will be no bias by the investigators with regard to the outcome. This is the most likely and quickest way to determine if this vaccine works and whether it can be helpful to most chordoma patients.

    Importantly, if you initially receive placebo you will have the option to "cross-over" to vaccine if your tumor grows. This means you can get the vaccine, at some point on the study, no matter which group you are assigned to.

16. **What are the chances of getting a placebo on the trial?**
    You have a 50% change of being assigned to placebo (1 out of 2 chance).

17. **When will I find out if I got the placebo?**
    You will not know, nor will your doctors at NCI know, if you are getting placebo while on the study. If your tumor begins to grow, your doctors will remove the "blinding" and find out if you were receiving placebo. If you were, you have the opportunity to receive the vaccine at that point.

18. **What happens if my tumor grows while on the trial?**
    For the first year, your tumor will be measured, but growth will not take you off trial unless you have new symptoms. After one year, if you have disease growth, you would have the study treatment stopped. If you were assigned to the placebo group, you would have the option to "cross-over" and receive the vaccine at that point.

19. **How and when will I know if the vaccine is helping?**

Your doctors at the NCI will go over each imaging scan with you at your visit and let you know if your tumor is shrinking, staying the same, or growing. This is done every 3 months after radiation for the first year, every 6 months during the second year, and yearly thereafter. Imaging can also be done earlier if you have new symptoms.

Any effect seen will be discussed with you, but it is important to note that your doctors at the NCI will not know if you are getting placebo or vaccine. If your tumor shrinks, it may be due to the combination of vaccine and radiation, but it also may be due only to the radiation. At the end of the study, we will compare the results and determine if radiation plus vaccine improved outcomes compared with radiation and placebo.

20. Are there any restrictions I'm going to have while on the trial?

You cannot take steroids during the study, except during radiation, if needed. Any new medications you plan to start should be discussed with the study team at NIH prior to the first dose to ensure there are no conflicts with the study.

Otherwise, there are no restrictions. We can work around scheduling conflicts for visits when possible.