Paper SA02

Going Through an AdCom With the FDA – The Ultimate Programming Experience

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ABSTRACT

An Advisory Committee meeting (AdCom) where clinical data is being reviewed and debated with an Expert Panel is in some case needed before the FDA makes a regulatory decision regarding the approval of a drug. The preparation process requires close cross-functional collaboration beyond Biometrics where the programming team has a crucial role. The programming team must prepare for all known possible questions in advance which could result in thousands of analyses. On the day of the AdCom, the programmers play a critical role in the success as they are expected to be able to produce validated analyses in a matter of minutes for any unexpected questions from the Expert Panel. There is no possibility to come back after the meeting with any clarification or additional data as the Expert Panel will proceed with voting right after the Q&A. This paper will share our experience and lessons learned from the programmers' perspective.

INTRODUCTION

An Advisory Committee (AdCom) meeting is held to provide the FDA with independent advice from a panel of outside experts on issues related to the development and evaluation of products regulated by the FDA either during the review process or after a product has been approved and marketed. The panel usually consists of several industry experts including 9 fixed members but also a statistician or epidemiologist. Most panels also include a consumer or industry representative. Although the expert panel give their advice to the agency it is the FDA who makes the final decision and they are not required to follow the guidance provided by the panel. The meeting is a public event and anyone, including journalists, competitor companies and patients, can attend and give their input at the meeting.[1]

Statistical programmers play a key role at the meeting but also from the beginning of the preparation process. The preparation for the meeting starts months in advance to be fully prepared to provide analyses to answer any questions during the meeting. First step in the preparation is to understand what an advisory committee meeting is and the agenda. Second, you must understand the role for you as a statistical programmer before and at the meeting and ensure you and your team fully understands the data, so you are able to create any unprepared analysis in a matter of minutes.

As a lead statistical programmer, you probably think that you know the submitted data inside out but while preparing for an AdCom meeting you will realize how much more there is to discover.

UNDERSTANDING THE ADVISORY COMMITTEE MEETING

The FDA will announce in advance if an Advisory Committee meeting is required. You will most likely already be in the preparation phase by then and it is recommended to start preparing as soon as possible if you expect a need for a meeting with the FDA.[2]

The meeting can take place either virtual or in-person. The Sponsor team will consist of a moderator, responders, triage and back room at the meeting. The number of responders, triage and back room will be decided by the Sponsor. The role of the responders will be to present the product and the efficacy and safety results. Responders can be respected industry key opinion leaders and regular employees at the Sponsor. Triage will be responsible for providing the right slides at the right time to the Responder during the Q&A session. They will have to be able to manage hundreds of slides and send it to the responder screen within seconds.

The people in the back room will be ready to support if a panelist ask for an analysis which has not already been prepared or is not in any of the triage slides. If this happens, the statistical programmer team will have an essential role in performing the analysis, ensure the validation and explain the output in a meaningful way for the responder to give back to the panel after a short break. All of this must happen within a matter of minutes.

It is highly recommended to find recordings of previous Advisory Committee meetings which can help you in understanding the format and type of questions.

MEETING AGENDA

The agenda for the meeting will be published by the agency in advance. The agenda can differ between different meetings depending on the needs.

The meeting will start with the opening remarks by the chair who will lead the meeting. The chair will ensure the agenda is followed and all panelists can have the opportunity to speak. The chair will also present the voting questions which will most likely be divided into a safety and efficacy voting. The panelists will be presented, and any conflict of interest will be disclosed. The sponsor will give a one-hour presentation following a Q&A session where the panelists can ask their questions. The length of the Q&A will usually be 15-30 minutes.

The FDA will also give a presentation which will include their review of the data. They can also decide to give a scientific presentation of the disease background or describe an unmet clinical need. There will also be a Q&A after the FDA session where the panelists can ask agency about their opinion. In this session the FDA can ask the Sponsor to provide the answer and the responders, triage and the back room will also have to pay full attention in this Q&A.
The meeting will also include an Open Public Hearing which allows the public, e.g. the patients, to give their views on the product.

In the end the panel will have a discussion led by the chair. After this discussion the panel will give their individual vote and have a chance to express their views on the product.

IN THE BACK ROOM

The programming team will be in the back room following the presentation and the Q&A session. Having at least three statistical programmers at the meeting is essential when a responder pushes an analysis request to the back room.

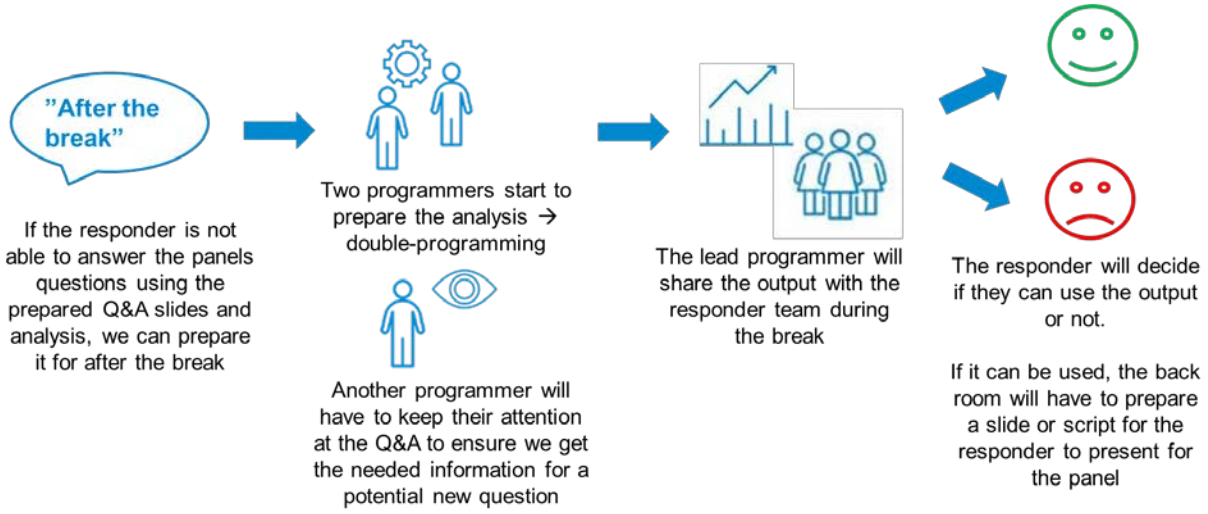
It is important to have roles and tasks defined before the meeting, so everyone knows exactly what to do. I would also recommend being careful not to bring too many programmers in the back room as it can be very disturbing as well.

The new analysis must first be discussed between the programmers to ensure alignment. The panelists are often specialized within a therapy area and the questions can be very specific or complex to understand. There will be no specifications or other written material to double check a request and it is therefore essential for all in the back room to follow the main room at any given time.

A request for a new analysis will require parallel double programming. Two programmers will start producing the requested analysis while at least one other keeps the attention to the main room in case, yet another request will come. In our setup we had one programmer using a set of standard macros to produce the output while another programmer would produce it without. We decided on this set up to be prepared for a scenario where the two outputs would not match. Although standard macros are robust they are also often very complex and time consuming to debug, and time is the main constraint in the back room for an AdCom meeting.

If there is a short break at any given point, the responders will rush to the back room for a short stop/go meeting. The analysis results will be presented to the responders if it is ready. The responder will have to make sure they understand the data and results before being comfortable to present it to the panel. In a case where the analysis is not ready the group will meet and discuss what options there are.

There also needs to be time considered for the analysis results to be prepared on a slide and QC'ed before handed over to the responder. Again, all of this can in some cases happen within 15-20 minutes.



WHAT CAN GO WRONG

The first thing the project lead programmer must consider is how to access the data if there is a server breakdown, WI-FI or local PC issues. Having a back up and a local access to the data and SAS is important. You should also prioritize to have all programs and outputs as well as clinical reports and patient profiles stored locally. In a case of a break down the panel will still have to do their voting and you risk not being able to answer all their questions.

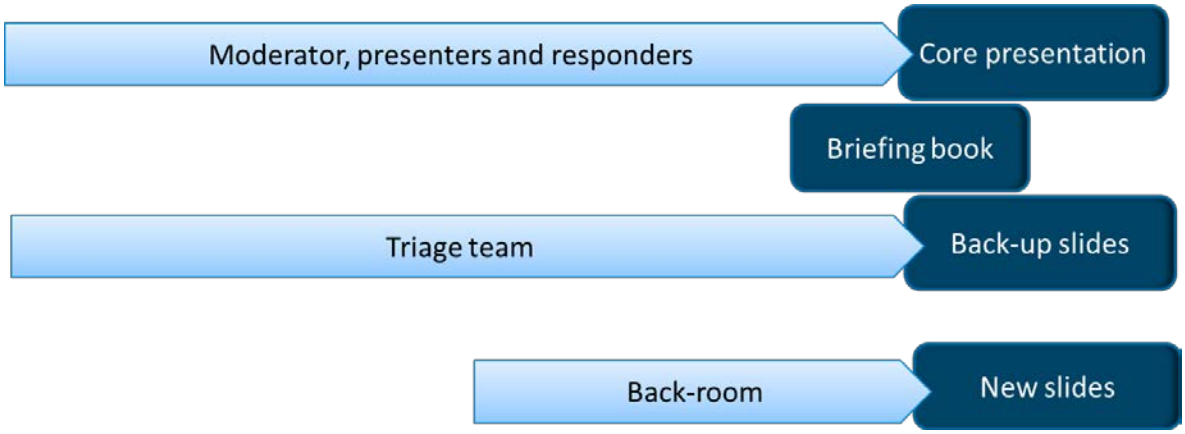
There is a risk that the panel will focus on one specific request at the day and you must ensure that all programmers have access to all information during the preparation, so no one ends up being the only one able to perform certain tasks or analysis. If many questions come to a specific task, then it is important that more people can start preparing in parallel. This will also make the team less fragile if a team member leaves the projects during the preparation.

PRACTICE AND PREPARE

The AdCom preparation team needs to prepare three essential deliverables:

- Core presentation
- Briefing book
- Back-up slides for Q&A

These deliverables are prepared in multiple parallel workstreams. Common for all are the need for input from the statistical programming team. The analysis and outputs presented in these documents can in some cases be the same as submitted in the clinical study reports, but it can also be new outputs. The Sponsor will be allowed to present data in another way e.g. another type of censoring or subgrouping, but only data available for the FDA can be used as they have to be able to replicate.



The programming team should be included and add input in the clinical discussions to prepare the core presentation and Q&A slides for as many scenarios as possible. As a project lead programmer this is an opportunity to add additional value by being part of the discussions where you can use your insight in the therapeutic area from a data perspective. You might be the only member of the discussion who knows the extent of analytical possibilities and this is the best time to make statistical programming visible to the stakeholders.
Being part of the preparation of all the above documents will also prepare the programming team in case any requests for new slides comes up during the AdCom meeting.

It is also recommended to use mock mimic the programming setup under pressure. Practicing at a mock meeting will help you find the weaknesses before the real panel does. At a mock meeting you should invite key opinion leaders and other specialists to a “in-role” setup where you practice as it was the real AdCom. Actual committee members receive the briefing book from the Sponsor but also one from the FDA prior to the real AdCom. You should provide a briefing book for the mock panel to ensure the mock panel have the same background information as the real panel.

You might find that you have to make a lot of changes after the first mock panel meeting but remember this is much better than receiving the negative feedback at the actual day of the AdCom.

The Sponsor will have to provide the FDA with the Sponsor briefing book in advance of the AdCom, but the FDA will also provide their briefing book to the Sponsor in advance of the meeting. This will give a good indication for the Sponsor on how the agency will present their review for the panel at the AdCom. As a statistical programmer, you will have a very short time to test the statistical analysis included in the FDA briefing book. In cases where the Sponsor does not agree with the results presented in the FDA briefing book, the Sponsor could provide the agency with clarification.

AFTER THE ADCOM

The process after the AdCom meeting will depend on the regulatory process specific for the product in scope for the meeting. If the AdCom meeting is held as part of a review process, there might be follow up questions from the FDA. The FDA do not have to follow the advice from the panel, but it is likely that a positive outcome will encourage the FDA to continue the review process as planned.
The programming team can continue to play a role in the review process by handling the requests from the FDA related to data or analysis or by adding input and analysis to the labelling negotiation.

CONCLUSION

Being involved in an AdCom as a project lead programmer is an amazing opportunity which is both personally and professionally rewarding and many skilled programmers go through their entire career without a chance like this. But you must be ready to work hard and prepare to skip weekend and evenings for long periods of time.

As a project lead programmer, you also must consider how many people you will need to be involved in the preparation and how many you will have active in the back room. I would recommend at least three but be careful not to include too many. Keep the people located in the back room to an absolute minimum and have supporting programmers ready virtually.

Start as to prepare and practice early as possible and take it seriously when practicing. Always practice “in-role” at the mock meeting to ensure you get to test the set-up. It is also recommended to practice a scenario where you are forced to use the local PC and printouts.

This is also an opportunity for you as a statistical programmer to step out of the shadow and show the clinical team and other stakeholders what we can offer and how much we actually do!

REFERENCES

[1] https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees
[2] Guidance for Industry Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members

ACKNOWLEDGMENTS

I would like to thank my colleagues Om Prakash Kumar and Shivam Srivastava for endless hours of support, relevant discussions and valuable inputs.

RECOMMENDED READING

Hall, P. FDA Advisory Committee Meetings– A Statistical Programmer's Survival Guide (2022)

CONTACT INFORMATION

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