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How to write a research protocol

Dr Boulate: So, hello everyone, this is a great pleasure to participate to this session today about "How to Write a Research Protocol." So, I would like to thank Doctor Bertolaccini for the organization, as well as the Europeans School of Oncology. So, I'm a thoracic surgeon from the department of thoracic surgery in the North Hospital, in Marseilles, and I'm PI of an epidemiological study, related to lung cancer screening. So, I have experience in writing protocols and management of research projects. So, please, if you have any question, I will be happy to answer it either during the presentation or immediately after. So, first of all, writing a research protocol is a really important part of a prospective or retrospective research project. And it takes time and if you are in your early career, it will transform you into a principal investigator, into a PI. So, it's a really important part of the research and you really have to take time to tackle all the aspects of the protocol. So, we'll follow this plan: so, we'll talk about the background and justification section; the objective and the research question, which is really one of the central parts of the research protocol; the methods and design and conduct. The data analysis part, which has to be inspected during the protocol writing. The ethics part, which is now really, really important; the timescale and the resources, and the reference and appendice part. So, to start, if I have a simple advice, at the bottom line is that to write a research protocol before to start to write it, you have to find a template and if possible, find the template of the application you want to answer to. And if it's possible, it will be easy and easier for you and more successful if you can find a successful application to the grant or other applications you want to do. So, the background and justification method is about why are you doing this research? And so, it may be clear in your head, but it has to be clear to anyone who is going to read this section. And sometimes, these are people which are not in your field and then, you have to explain why, clearly why you want to do this research and this protocol. So, this is a typical way to do it. Usually, you start with the knowledge part, what is established in the literature or what is the common knowledge about the question you want to tackle. Then, you go to the uncertainty part, in which you are going to explain which are the unknown aspects, which are the gap in knowledge. And then, at the end, you are going to explain your hypothesis. And this is an important part to write your hypothesis which may be true or false, but the aim of your protocol is going to be to answer whether your hypothesis is right or wrong. So, the literature part is really important. You really have to well know all the literature about the subject of your protocol in order to really position your protocol at the edge of the knowledge. And then, really, if you want to explain clearly what is going to be your research, you have to determine whether your research has already been done and you want to redo it or you want to do an original research. And to answer this question, you really have to well know the literature. And another advice is that you really have to discuss the positioning of your research with experts and ideally, either in your department or in other departments. But really, you have to position the question and avoid to reduce things that is already known and that is already knowledge. When you write your introduction or your background section, really, you have to be

logical in the sequence of the sentence you are writing and it will really avoid criticism. And you really, another advice is that you have to go from wide aspects of the field to specific aspects of the question. And really, you have to be able to explain to anyone, why are you doing this research. For instance, if you work on lung cancer, for instance, and you want to identify a population to make a lung cancer screening, for instance, you have to explain why lung cancer is an important topic. You have to explain why lung cancer screening is an important topic, what is known, what remains unknown. And what can help you in your explanation it's to read the recommendations in this field. For instance, if you read the recommendation about lung cancer screening, the European recommendation, then you will write, you will find which are the questions and answers and the research priority in this field. Then, at the end, you write your hypothesis with a simple sentence. We hypothesize that et cetera, et cetera and it might be right or wrong. So, the hypothesis, doesn't have to be right but it is going to be tested by research. Then, you go to the objective part and the objective part is really central. And this is a decision you have to choose which is your objective. And this is based, this is a logical step after the background and justification. And when you have chosen the objective, the method and the feasibility, have to make the answer to the objective feasible. And the objective is really a central part of the research protocol. And all your research will have one goal, is to answer to the objective. So, this is a central decision, when you are writing a protocol and it has to test your hypothesis and the method, and the feasibility part of your research protocol, has to reach the objective. And your research is going to be judged based on your result and whether your result, answer to the objective that you wrote at the end of your introduction. And when you are writing a research protocol and when you are implementing it in the real life, you will have to take a lot of decisions about study type, about timelines, about all aspects and the only repair you have to take decision, is it going to help me to reach the objective or not? And to make it simple, you can try the lift test with the director of your hospital. So, if you talk to the director of the hospital in a lift and he may ask you, "So, David, what is this protocol I read about it? Can you tell me about what is this?" And you have to be able to answer with a simple sentence; the objective is to measure lung cancer prevalence in a specific population, for instance. And it has to be really clear and you are going to repeat the objective of your research when you are going to hire people to make a team, when you are going to find funding et cetera, the objective is really important. And often, the objectives are known in your field. So, this is the primary objective. This is really, really your ripper in the research. So, if you have any question, you can ask it now. Okay, let's go. So, now the method. The method is a consequence of the objective and the background method. So, you don't have to choose the method before have chosen your objective. So, this is important in how you are going to build your protocol, because, for instance, things may be really simpler to answer your question. Sometimes if you want, for instance, to determine whether, for instance, if you want to determine whether an aortic arrhythmia screening among patients with lung cancer, for instance, is interesting. You don't have to do a prospective study, et cetera. You may only do a retrospective study and using the CT, or the PET CT, for instance, and it will be easier. So, if your question is really to know whether what is the prevalence, or is there an interest to detect aortic aneurism in patients who smoked and have lung cancer. So, you can do it easily. And if you want to do a prospective study on this, you will really waste your time, for instance. So, the method is adapted to the objective. And then, you are going to choose, which is the best study type. And to answer your question, and for this, maybe, the best is to discuss it with a methodologist. So, you are not... I'm not an expert for instance, but I don't have to be an expert in methodology. And I'm going to discuss with experts what is the best way to answer my question. So, if you are a medical doctor or a surgeon and you want to do clinical research, you don't have to be an expert in methodology to build a research. So, you are going to tell, "Okay this is my question, here is my material. And what is the best study I can do?" And then, you are going to choose, so, this is a really important part, you are going to choose endpoints. So, you have your objectives, which is to determine whether this treatment is better than this one or is equal. And your endpoint is the hard data you are going to provide to answer your question. And so, this has to be usually the quantitative endpoint. And usually, these are guidelines in your field, that explain which are the best endpoints to choose when you want to test a drug, for instance. Disease-free survival, overall survival? And so, in cardiovascular disease, in permanent hypertension this is 6-

min walk distance, or time to clinical worsening. So, it depends in your field. And usually, there is a recommendation, European recommendation, or national recommendation, to choose your endpoints. And it will be really important to well-define your endpoints because when you are going to want to publish your results if you, for instance, you do a real-life study about mouth washing before thoracic surgery, and if your outcome is a re-intubation, for instance, but you will only be able to publish in an intensive care journal, instead of a surgical journal or in the JAMA or et cetera. And so, you are going to waste a lot of time, a lot of energy to build your prospective randomized study. And at the end, if the endpoint is not well-chosen, you will not be able to publish in the journal you want. So, read the recommendations from the journal and this is same for the study type, as there is NICE in the JAMA, for instance, in the JAMA network, in the guide for authors I will show you later, there are all the recommendations to follow, to report data based on the study type. I will show you next. So, then, you are going to choose the variables. You are going to make sure the methodologist is okay with the way of data collection and because it will ease the extraction. So, as a step, you have to discuss with the methodologist and with the data manager and with the statistician who is going to do the analysis to make sure the data you are going to collect are in the right form and will be easily extracted and analyzed. And then, you can start to discuss about the analysis plan and you are going to avoid pitfalls. For instance, if you are doing all your tables, you are not going to forget sex, for instance, or age, which are really easy or trivial data. But if you don't do it during the writing of the protocol, at the end, if you have 500 patients, you have to do manually the extraction of the sex and you will lose several days to do this. So, really talk with the data analyst and the epidemiologist to well prepare this section. So, this is for instance, the jamanetwork.com and here, you can see on the left-hand side, you have the oldest study type. And if you click on it, you will have the recommendations for the reporting of this. And it may be really helpful to write your protocol in the line, directing the line to publish it. Then, you have to choose in the method part, the conduct. So, how you are going to collect the data. Once you have chosen the type and the data you are going to collect, and you have to define the visits. So, the visits, this is important, how long it will take, are the visits a separate visit from the usual patient's management or whether these are research visits additional to the current patient care. You have to define the kind of intervention. If this is an interventional study and not an observational study. You have to choose whether there is randomization, if you want to randomize a time of infusion, or after infusion or et cetera. And you have to define the timescale, what is feasible in real-life and to also determine where you are going to perform the research, if this is clinical research, whether it is in a hospital department, outpatient visit, research department, in a truck, for instance, or wherever you want but you have to define where, when, how long it takes each visit. And you also have to determine the total length of your protocol, because this is a really important part, when you are going to deliver, this has to be adapted to the grant you are answering, to the kind of application you are doing. Then, you have to prepare the data collection. So now, today, so, it's cool if you can do it without any paper. So, you can find, either internally to your institution or externally to your institution, you can find data managers that can create Electronic Case Report Form. The ECRF. And you can build it, so, you first do a first draft on the Word, for instance, on a Word document, and then, we'll transform it. And you have to build it with the data manager and make sure you have all the data you need. It feels well, when you are using it, you have to test it. You have to make a test by other people, et cetera. Then, it has to be okay in format. In terms of format, it has to be okay with the data, with the statistician and the guy who is going to analyze your data and make sure the extraction is going to be easy, et cetera. Then, you have to, like you're a PI, you have to create your team and determine who is doing what. And this is really important. Who is doing the inclusion? Who is doing the pre-screening? Who is doing the screening? Who is calling back the patient for the follow-up? Who is doing blood draw? Who is doing the CT? Who is going to interpret the CT? And who is going to report the data on the CRF? So, all these things are really important and you have to explain your project to all these people. So, this is the project, the main objective is this, it will take this time, we have this budget, there are these kinds of patients. And if you can explain clearly your protocol, then, you are going to have motivated people to work with you. And it's really important to communicate when you are building your protocol and to have feedback from the future people who are going to be part of your team, to make sure they well

understand the project. You have all the same goal, which is the main objective. And so, this is an important part of the protocol that you will start to create your team. Then, you are going, of course, to determine the number of patients based on the pool you want, what you want to prove, which are your objectives, et cetera. So, this is a part you do with the statistician. And to determine the follow-up duration of each patient. Then, you have to find a budget. So, usually, you are writing a protocol to have budget or it may be also to have ethical approval, or it may be... So, the budget part is really important. Sometimes, what I recommend is to start to have a budget in a national grant or in like seed grants for early career or internal to your institution. So, it's very nice to have preliminary data and start a small protocol, like one year or less, that can provide you preliminary data. And that you are going to be... that you are going to use for bigger applications. Also, for the budget, you have to clearly explain who is doing what and finally, the budget is based on your method. And you are going, sometimes, to repeat the application of the same protocol, to different funding possibilities. Then, you have to explain in the method part, not explain, but you have to make sure that you have the support of your chair department and of the administration, to make sure you are going to have all the place available, that the manpower is going to be okay. That you are going to have time to perform your research. This is really important, if you are PI of a study, you have to include one patient per day or two patients per day or one patient every week, if these are rare patients. So, you are going to have time to do the research and get the data and have good qualities, this is really important at this stage, to make sure the organization, you have the support of your department and the support of your administration. So, you will have to do a lot of choices, to adapt the methods to the objective. And then, what I will recommend, is to be in the Medawar Zone. So, to choose an easy objective that is going to be easy to reach. For instance, I wanted, in my experience, I wanted to do a lung cancer screening among patients with arterial sclerosis and who smoked. And I had to choose the objective. And I knew the objective was to perform an epidemiological cohort and the method to measure the prevalence of lung cancer, for instance, in this population was to do lung cancer screening. So, lung cancer screening is a method to achieve my objective, which is to describe the prevalence of lung cancer in a dedicated population. And I chose the population. For instance, I was in a hospital with a lot of cardiovascular disease and lung cancer diseases. And then, so, I chose to do lung cancer screening in the population which was abundant in my environment. So, it's easy for me, every day, to include one or two patients who are coming to the hospital in the outpatient visit. So, this is easy for me. This is not too easy to have pay-off, but this is not too difficult and then, I am in the Medawar Zone. It means that it's neither too easy, neither too difficult and I will do this research to the end because my gal is simple to understand and I have a lot of patients. Okay? And for instance, another example, here was that to include patients to do a lung cancer screening research and we wanted to have a Biobank, for instance, so, you have to schedule the low-dose CT and the biobanking. We wanted to have like a microbiota, gut microbiota. So, what we did to make sure patients had not too much constraint. So, we made sure there is no too much constraint, sorry, for the patients. So, we told them... Those are all cardiovascular patients, for instance. So, we told them the next time you are coming back to the hospital to see your cardiovascular surgeon or your vascular surgeon or your cardiologists, for instance, it's always every six months. So, we say, "This day, we are going to do the lung cancer screening. We're going to do the low-dose CT. We're going to do the biobank this day." And to make sure the patient accepts to be enrolled in the protocol. And what we had to do in the protocol it was just to enlarge the delay between the inclusion and the low-dose CT and biobanking. And when you explain it to patients it's easy for them to say, "Okay, the next time I go back to the hospital, I will do my phenotyping, my CT and my blood drawn. Okay, it's easy for me, there is no constraint." And so, it makes your research really easy. So, this kind of decision can really help. And during, when you are building your protocol and you have to take time to imagine what is going to be the inclusion, for instance, and what is going to make your research, your protocol is success. If you have questions.

Dr Bertolaccini: David, we have two questions from the attendees. The first is regarding the electronic collecting of data, which platform do you prefer? An Excel, simply, or the Red Cap Platform or other platforms?

Dr Boulate: So, Excel is not for databases. So, clearly, it's dangerous because there are limited numbers of lines and it's not done for data collection. So, either you can use Red Cap which is an open-source platform but which is known by a lot of research departments in a lot of institutions, for instance, in Marseilles, in the public hospitals, in Marseilles. So, we have this, we have Red Cap. But you cannot do everything with Red Cap. So, it's a good start. If you are doing a simple research, it will be very nice. For instance, I am a principal investigator in lung cancer screening and then, I have to follow-up nodules, for instance, and then it's a more complex architecture of the CRF, which is conditional, et cetera, with more complex extraction. And then, I used the private, so, you can find on internet, in your country or in Europe there are startups or there are industries that can help you to build your CRF. So, minimal is Red Cap, but you can... There are private societies also that you can find. Mine is Easy CRF. It's the name of the... This is one guy, he's a doctor, he's only doing data management. And so, it's really flexible. You can call him. So, I would like to have this, this and do this, this and then at the end, when you are entering your data in a patient visit, it's really easy because you built everything and you built it with the radiologist, for the report of the radio, you build it with a biologist for report of the Bio-part, and all the doctors can collect the clinical data. And even the other people of the team can write all the questionnaires, the quality-of-life questionnaires, et cetera. And you can even use it with an interface for the patient, like an iPad, for instance, and the patient can answer their own questions. And it's all in the database.

Dr Bertolaccini: An anonymous attendee asked a good number of a team for a research protocol, 10 people, 5 people?

Dr Boulate: Yeah, I think, sure you cannot do it alone. That's for sure. You cannot be an expert in biology, in biobanking, in radiology, et cetera, in drug and pharmacokinetics, et cetera. So, you have to build a team. And the best thing to do is, you have to talk of your protocol to people with whom you have good relationship. And say, okay, you know I'm writing a protocol and then there is this part and who do you think may be interested for following me to write it. And I think, if you include your partners and the people of your team when you are writing the protocol at the beginning, it will be easier to get the job done for the protocol and to answer to your objective. So, I think a good size is... I think it's not a lot. I think it's... So, you have to... For your project, it's in general for the project success, you have to have a sponsor. So, what is important is that in your institution you have like a guy with weight that will help you to talk to the sponsor, to the director of research, of you have to talk to the director of research and they have to support you. You have to have support. This is not really the team but this is the environment that is going to help you. Then, you have to find the investigators. So, who is going to collect the data? Who's going to see the patient? Who is going to include the patients? And usually, it depends on your protocol. If it is a once a week, you can do it alone. You can include the patient alone. If it's three or four patients a week, for instance, it's a full-time job, then, you have to talk with the head of the department. Say, "Okay, we'll do this project for this time. We have to include this number of patients, for this time. And then, I need one, two, three four, five, six, seven, ten, if it's multicentric." So, it may be a lot, and then you have to have people to help you to collect the data. So, I think it, and to do the biobanking and people, I think it's important to be able to talk to people every day, for each aspect of the research, of the protocol. So, it depends on the number of tasks but I think, one people referring for a task who is going to manage his team is adapted. But the smaller is better. Smaller is better, but if you need several competencies you have to have one person per competence.

Dr Bertolaccini: Thank you, David.

Dr Boulate: Shall we continue?

Dr Bertolaccini: Yes.

Dr Boulate: It's almost the end. So, data analysis, this is a really important part because these are the results. So, these are the results. And the result and the paper, for instance, is judged based on the results. So, this is a really important part and you have to anticipate all the bias. And many, if you are doing prospective

research, you have really to avoid, to get biased enter, in your research. If you are doing retrospective protocols, you are going to try to make the bias out. But when you are doing prospective research, you are trying to avoid the bias to enter in your study. And I have an example, for instance. So, I was responsible to test the serology of 3500 patients in two hospitals during the first COVID wave. And so, the link of the screen was off. So, we did a serological test for all the healthcare providers into hospitals. So, it was more than 3000 tests. So, it was two tests. And at 4-week, separated from 4 weeks. And we wanted to test exposed healthcare providers versus non-exposed administration, healthcare providers, et cetera, to determine whether if you work close to patients with COVID whether you are at higher-risk or not to get COVID. So, to determine the eventual risk factor to get a COVID infection based on serological tests. So, to do the blood drawn for all the people we needed 4-weeks. And during 4 weeks, there were exposures. So, during one meeting, one guy said, "Well, sorry but if you test all the people at risk at the beginning, and the people not at risk at the end of the 4 weeks, the people more exposed are going to be exposed less time. So, there is a bias in your results. You are going not to find the difference if there is one. So, these are simple things that may really have impact on research. So, you really have to talk about your proposal. You have to share it and to get feedback, to avoid bias. Okay? Then, you have to determine whether there is an intermediate analysis or not. You really, you have to keep it as simple as possible. So, if it's not necessary, don't do that. And you have to determine secondary objectives. So, secondary objectives are really secondary objectives, but it may help you to get preliminary data for another or for the next study. So, this is an important part, but all you choose, you really have to focus on your primary objective. For the data analysis what is really important in all the fields of science and even in medicine is the quality of the data. So, really, if you have good quality of data then, you are going to be able to interpret your results really clearly. If the quality is not good, this is going to be a problem and headache. So, what is really important when you are building your protocol in the data analysis part, anticipate how you are going to evaluate the quality of the data and then, you may have to simplify the acquisition or et cetera, in order to have a perfect quality. And the advice is, of course, to choose the declaration, which is really feasible, and for which you are going to have the highest percent of fulfillness. And when you are writing the questionnaires, for instance, the questionnaires to the patient, to find risk factors or to collect secondary effects of drugs, for instance, or exposure or whatever. When you are going to give these questionnaires to the patients, please make it read to your family, to your friends, to everyone, to patients from really different fields, educated, uneducated, because they will give you feedbacks. They will not understand some things, et cetera, and really it will make your data collection better. So, this is an important part of the preparation of the data analysis, preparing the questionnaires. Then, it takes a legal aspect. So, this is really general. So, of course, this is really important. You have to classify your research interventional and interventional on human, or on existing data, it depends on your country, of course, and your continent. So, usually you have a research department who is going to help you in this area. My advice to you, if you can answer objectives with a simple protocol without too much authorization, it's better for you because this is less work. If you want to test a new drug, for instance, you will have to really have a lot of authorizations and you have to take it into account in your timeline. In Europe, there is the GDPR, the General Data Protection Regulation. So, you have to declare all the data, the data collection, even for screening, pre-screening, et cetera. And of course, you have to prepare an information note to the patients, in France it's oral and written. And you have to prepare a written consent and get of course, an IRB or ethical authorization. And it may take time, too. So, you can, once your protocol is validated by your team and at your institution you can start to obtain these agreements, ethical agreements in order to be able to start your protocol as soon as possible. Then, the scan line, to prepare it, usually what is asked is a Gantt diagram. I will show you an example. So, the Gantt diagram allows us to have a clear view of the timelines and to determine which task you have to start first not to have limiting tasks. For instance, if you have to obtain a freezer, a minus 80-degree freezer, sometimes, it will take one month or two months and you will not be able to start your protocol once you don't have your freezer. So, anticipate it and try to get this one or that in advance so as to start your protocol. For each task, you can do a Gantt diagram for each visit, each task. And put it together to have a wide view and then, do a global Gantt diagram to make sure all is okay and to

have your agenda. If you are doing something that has never been done before or something in which you don't have any experience, make sure it will take always more time that you expect. So, it's at least 1.5 times or 2 times longer than what you expect. So, be prepared. And the final line is, if your research is highly exploratory, for instance, we did the lung cancer screening program for research. We learn how to do lung cancer screening into the research protocol. So, you have to start with an organization, with a team. And if it is highly exploratory, you have to adapt. There are two big types of managements. There is long-term management. If it is some single-task, we have done a lot, like building cars, for instance, if you have a Ferrari, for instance you know how to build a Ferrari and it will be easy to do it. And then, you can prepare all the steps and do quality control every two months. But if you are going to do something which is exploratory, then, you have to do adaptive management, short-term management and make sure you are going to have to fix a lot of details and take decisions. Because for instance, the treatment has a secondary effect, or is a very low-dose CT organization, doesn't work, et cetera. So, you can prepare to do weekly meetings to fix all the other problems. And you have to tell it to your team. So, okay. You tell them, "Okay, we start but we don't know what is going to happen. We try to anticipate all the pitfalls but we know they are going to have problems. So, don't worry. Each time there is a problem you fix it. And if people are prepared, it's okay. And then, you build on the errors and you fix all the problems when you start the protocol." So, you write your protocol and you do it. And if there are uncertainties, you can write it in your protocol or if it doesn't work, you are going to meet and to adapt. So, this is a Gantt diagram. So, a lot of people know what it is but a lot of people don't know. So, there's a nice tutorial on YouTube. And usually, you write a date for the starting, you have a task. So, each line is a task. There is a starting, is the end of the task. And the days, in here, for instance, so, you have your protocol starting here with a visit-0 visit-1 and all the follow up. And, you know your study is going to end in May, 2022. And then, you have a clear vision of your protocol and then, into each, and you can redo it for each task to make sure, for instance, you have 10 minutes for explaining the protocol. You have 5 minutes to make sure, at the beginning, 5 minutes to make sure that there is inclusion and no-exclusion criteria. 10 minutes to explain the protocol, 10 minutes to make the signature, et cetera. So, the resources are really important. So, you have institutional resources. So, sponsor, we talked about it, to make sure the research direction, administration, you had the background, it is okay with your protocol and the time that it will take and the people that will engage. Maybe, you have to hire people, either internally from your institution or from outside your institution. For instance, you can hire a nurse to make her in your research department, for instance. Maybe, a nice evolution in a career. You, of course, have to find financial support. And often when you have one authorization, what I recommend is to start with a local public grant and then, it will give you credibility to go to talk to private entities or et cetera. As the matter is important, so, we talked about the freezer, it may be really important. The tubes to collect the biobanking, the drugs, if you use drugs, et cetera, the transportation. So, you have to planify everything to make sure to be able to get all the material you will need a to list it and to fund it. Then, the participants, it's really important to anticipate and prepare how you are going to screen, pre-screen the patients from databases, from outpatient visits, from staff meetings. So, how you're going to source your patient. And I think, today, it's important to talk with the IT department, to make your life easier. For instance, to tag electronically patients' folder who are participating to the study or to pre-screen the patients. It will really make your life easier. Also, in Easy CRF, in electronic CRF, you can get emails when there is an event, for instance, a positive scan, for example, a positive CT scan. Then, you can get an email to take the patient in charge. So, it may really help you to do your protocol. And finally, so, what to put in the reference and the appendix? So, the preliminary data. So, I didn't talk about it in the introduction section, but really if you have preliminary data from your institution or your team, it is really going to help you to get your funding and make your application successful, because preliminary data really gives you credibility. And then, maybe, retrospective data. For instance, for my application for lung cancer screening, I did a preliminary study on lung cancer screening, on the outcomes after surgery in patients with criteria for lung cancer screening. I did an abstract and I put it in my application. So, they saw I had preliminary data. I already worked on this subject and publish it. If you can, for one or two weeks, determine the number of patients that may be including in your protocol or the

acceptability form the patients, if we do this protocol, would you agree or not? And then, you provide this, it may really help you to get funding. So, add figures to your protocol, when you explain, you can put a Gantt diagram, you can do a scheme of your protocol. It really will help. Or if you have a pathophysiological hypothesis, you can draw it and it will really help the readers to understand the important aspects of your justification and of your protocol. Then, of course, literary reference, recommendations. So, it's important to explain that this study has to be done because this is a recommendation. You have to put questionnaires that have been read by a lot of people. And I really feel if you already have it, it will increase your chance to get funding, if you already have the ethical approval. So, in conclusion, I would say take a template, write your protocol. You don't have to be an expert, but you have to be a PI. So, you are the chieftain. You are the coach. Then, you discuss and you share your protocol with the important people for each aspect, all the experts. Then, you add that to your protocol based on the feedback. So, you have to be flexible. You have to be open. Maybe, your primary ID was not, was good but it has already been done or you can do it in an easier way. So, you have to really adapt what you're seeing, you're feeling to the real life and to the expert view, and you are going to progress. Then, all your protocol has to be really coherent. And you have to have clarity. It means that if you are, for instance, in the secondary objective, or primary objective, you want to talk about quality-of-life, you have to put it in the introduction in the literature method, for instance, quality-of-life is the limit for this treatment. So, we want to test another one and then, in your secondary objectives, you are going to put the do quality-of-life evaluation. So, we understand it. If you don't put it in the introduction, it's not clear. We don't know why you want to do this. And so, it has to be really coherent. You can publish your protocol. I think once it's funded, you launch it. You, adapt all the aspects and it's a stable protocol. You can publish it because it will help you to publish the results, at the end, if you want to get to high impact factor journals. And then, at the end, be a PI. And this is a very nice book to know, to learn how to write to the prosaic form that may help you to have a very nice protocol. Thank you very much.

Dr Bertolaccini: Many thanks, David. We have not enough time to other questions from the attendees but if the attendees want, could write the question and you will ask to them. So, many thanks to everybody and happy Easter.

Dr Boulate: Bye.