Presidenza del Consiglio dei Ministri

COMITATO NAZIONALE
PER LA BIOETICA

MOTION

VACCINES AND PLACEBO

9 July 2021

There are now four SARS-CoV-2 vaccines available for Europe, as well as others in Russia and China that are still under investigation. However, there are many vaccines in the process of various stages of development and above all there is still room for new vaccines, taking into account the need to counter new variants of the virus which can develop in Europe or come from other parts of the world such as for example the "delta" variant of Indian origin.

The availability of vaccines, which have already proven their efficacy in controlled clinical trials as well as on many millions of people, also raises new ethical issues in the implementation of phase 3 clinical trial protocols[1] regarding the new vaccines, necessary for approval by the regulatory authorities. The Declaration of Helsinki is very clear in requiring that, when active drugs do already exist for a given indication, the best medicinal product available should be used as a control, not a placebo[2].

Therefore, even in the case of vaccines, the question arises as to whether it is right to use a placebo.

In some cases, it is possible. For example, no approved vaccine has been studied in young people under 12 years of age. It is evident that in this study not only is it right, but it is necessary to use placebo, especially as there are relatively few cases of symptomatic disease in young people and therefore without the use of placebo it would probably take more time and require more participants. On the other hand, the use of placebo for subjects over 12 years of age is not acceptable because results already exist and therefore an already available vaccine must be used as a control. This provides a double advantage: on the one hand, it avoids exposing people to unnecessary risk and on the other it allows collection of comparative results, that is, to determine in the end if the two vaccines are similar or if one is better than the other. Clearly this makes the study more complicated due to the difficulty of obtaining the control vaccine which, however, must necessarily be made available.

A comparative study may not always be in the interest of the industry developing the vaccine, but it is important for the community, which has the right to know the different efficacy of products that have the same purpose.

For placebo-controlled studies that are in the early stages, changes in the protocol must be made to include an available vaccine in place of the placebo.

At the end of the study, a decision may be taken to continue phase 3 in order to obtain other information. For example, in this way it is possible to see if toxicity occurs over a period of months, or to follow the evolution of various types of immunity over time. However, it cannot be forgotten that the group of participants who were treated with placebo continues to be exposed to the risk of infection and also, albeit less likely, to the risk of severe disease and mortality. Therefore, the need arises to stop the study and therefore interrupt the double-blind procedure[3], because those who received the placebo have the right to undergo vaccination and to be given priority having exposed themselves to an essential

[1] The phase 3 study is used to determine how effective the drug is, whether it has more benefits than similar drugs already on the market and what the relationship between risk and benefit is. In this case, there are many thousands of “enrolled” patients.

[2] Placebo is a pharmacologically inert substance that can be administered to participants in clinical trials to make comparisons with active medications when no other active treatments exist.

[3] Double-blind is a study in which neither the investigators nor the participants know the type of treatment assigned (in this case, whether it is vaccine or placebo).

risk in order to obtain reliable results. At the start of the study, it was not known whether the vaccine would be effective, but in the end results are available. The study can therefore continue provided that the subjects treated with placebo are vaccinated.

A possible exception to this solution, which must in any case be considered a priority, may consist in subjects' deciding to continue receiving the placebo, also given the solidarity-related importance that this choice could have. This can only take place under two conditions: obtaining a new informed consent that also attests the awareness of these subjects of the risks to which they subject themselves and those with whom they come into contact and evidence that continuation of the placebo study is scientifically appropriate and highly significant.

Lastly it should be emphasised that continuation of the study with administration of placebo represents in any case an amendment to the experimental protocol and as such must be submitted for evaluation to an ethics committee for clinical trials.

For those who remain in the placebo control group, treatments should be available to mitigate possible viral infection.

Recommendations

1. The ICB recommends that the testing of new vaccines in phase 3 of trials is to be carried out not using a placebo as a control, but an already available vaccine and it invites Ethics Committees to monitor and ensure that this recommendation is respected in trials.

2. Regarding placebo-controlled studies that are nearing completion the Committee believes that they should not be routinely prolonged; their extension may however be acceptable on obtaining a new informed consent, subject to approval by the relevant Ethics Committee for modification of the experimental protocol and based on scientific relevance.

3. The ICB recommends that in the locations where new vaccines are being studied, the most effective existing treatments to stop contagion and counter the infection are to be made available.

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The draft was drawn up by Profs. Silvio Garattini and Cinzia Caporale.

The motion was approved in the plenary session on 8 July 2021 by Profs: Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Antonio Da Re, Lorenzo d'Avack, Mario De Curtis, Riccardo Di Segni, Gianpaolo Donzelli, Silvio Garattini, Mariapia Garavaglia, Marianna Gensabella, Laura Palazzani, Tamar Pitch, Luca Savarino, Monica Toraldo di Francia.

Despite their not having the right to vote assent was given by: Dr. Maurizio Benato, the delegate for the President of the National Federation of MDs and Dentists Colleges; Dr. Carla Bernasconi, the delegate for the President of the National Federation of the Orders of Italian Veterinarians; Dr. Amedeo Cesta, the delegate for the President of the National Research Council; Prof. Paola Di Giulio,

the delegate for the President of the Superior Health Council; Prof. Carlo Petrini, the delegate for the President of the National Institute of Health.

Profs: Maurizio Mori, Assunta Morresi, Lucio Romano, Lucetta Scaraffia, Grazia Zuffa, absent at the time of voting, subsequently assented.

Profs: Carlo Caltagirone, Bruno Dallapiccola, Massimo Sargiacomo, absent from the plenary session, subsequently assented.