

## **Adaptive Clinical Trials: Are the Regulatory Regimes of India and the U.S. Ready?**

**Panelist: D A Prasanna, Ecron Acunova**

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His Excellency Dr. Wisner, Dr. Rubin Paul, Distinguished Panel and friends,

- A. Many thanks to Patton Boggs for inviting me to today's discussion. I would like to thank a few people who have given me valuable inputs for this task. Firstly, Dr. Kazem Kazempour Chief Bio-Statistician of Ecron Acunova's partner, Amarex, and a former FDA Biostatistician. Secondly, Dr. Ernst Bluemner, Chief Biostatistician of Ecron Acunova, who has worked with the legendary Prof. Bauer of Austria on adaptive trials in Europe. Dr. A. S. Arvind, Strategic Advisor to Ecron Acunova, who has registered biological products for Biocon in India based on adaptive trials. While the credit for some of what I share is theirs, in case you find any inconsistency, in my thought process, the fault is all mine!
- B. The main idea is to start the first stage of a trial and then to complete further stages. All the stages can be combined for a final analysis. The simple case is a two-stage trial. After the first stage, you perform an interim analysis and you conduct a second stage of the trial. The advantage is that you can adjust original assumptions to more precise assumptions for the conduct of the second stage. As you combine the data of the different stages there are new possibilities, but also certain dangers.
- C. Adaptive clinical trial is feasible and important, because:
1. It may reduce the number of subjects required for a clinical trial, without reducing the statistical power,
  2. It will expedite time to market as it justifies the necessary changes based on real time data, and allows the sponsor to use adapt their design based on real time data.
  3. It will reduce the cost of conducting trials, as the sponsor will learn if their clinical product (i.e., drug, device, vaccine,..) is working /is not working.
    - a. If it works, based on interim analysis, the sponsor can justify to put more resources and get it to market faster,
    - b. If the early data demonstrate it doesn't work, the sponsor will have the choice to modify the trial design, their patient population, the dose, the sample size,... or even stop the trial and save time and money.

D. With many distinguished practitioners here, I will not go into the statistical aspects of adaptive clinical trials. However, I will focus on how a CRO should be prepared to play its role in managing a study using adaptive clinical trial design. And try and answer the experience of adaptive clinical trial design in the Indian context.

E. Adaptive clinical trial design requires the CRO

1. Bio-statistics team to simulate scenarios and analyze aspects of validity, significance, power, p-value combination, error analysis etc. In the last 20 years, a huge research effort has gone into the subject. Based on that research, a great variety of validated methods for adaptive designs are available. CRO needs to have these software tools, use it for simulation and have the competence to interpret them. Dr. Bluemner in Acunova uses ADDPLAN software for data driven re-estimation of sample size.
2. Regulatory team's ability to communicate, convince and get permission of regulatory authorities for the 2<sup>nd</sup> stage protocol, which is modified on the basis of interim analysis. Acunova's team has handled it in multiple countries across continents, not without challenges!
3. Clinical operations team has adequate monitoring controls for confidentiality, randomization, and blinding. Has drug distribution logistics to implement adaptive design decisions. Has the managerial ability to get several stake holders aligned in multiple sites in several countries.

F. Indian context in adaptive clinical trial design, I would like to devote the next few minutes:

1. Data from a study conducted using adaptive clinical trial design, is any difficulty anticipated in getting marketing authorization in India from DCGI? No, pre-approval by other regulators particularly in Europe and US makes a big positive impact on the DCGI's positive decision.
2. A study designed using adaptive clinical trial, is any difficulty anticipated in getting DCGI approval to conduct such a trial in India? If the same trial is approved previously by FDA or EMA, then DCGI approval should not be a problem. In the past DCGI has approved adaptive trials in that scenario. If the trial is filed 'de-novo' in India then DCGI approval could be an issue as the DCGI has not released any formal guidance on review of such trials. Hence DCGI is going to review on a case-by-case basis.

G. To close my address, I would like to cite two 'de-novo' biologics studies in India one of which Ecron Acunova participated.

1. Anti EGFR 4 arm study in head & neck cancer: DCGI agreed to a design where a smaller sample size was chosen on the basis that, if safety or

efficacy was not statistically significant in the smaller sample, the sample size will be increased by 3 times. After interim analysis, drug was approved.

2. MMF+ ACE 3 arm study: DCGI agreed to an adaptive trial design of 100 patients in each arm in stage one and 200 patients in each arm in stage 2. Interim analysis required the sponsor to go to stage 2. After completion of stage 2, due to superiority not being established by data, the drug was not approved.

I would like to conclude that there is a growing acceptance of adaptive clinical trials when scientifically designed and correctly implemented, be it India, Germany or USA.

*D A Prasanna*

Chairman and Founder

Ecron Acunova CRO

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