The art of clinical trial design in pulmonary fibrosis

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Eligibility criteria for clinical trials need critical consideration https://bit.ly/3mWl8Lz

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The design of clinical trials is an art on its own. There are numerous, partially conflicting aspects a clinical trial has to satisfy. First and most importantly, the trial, especially in phase III trials, should ideally demonstrate a statistically significant effect of the drug under investigation on a clinically relevant primary endpoint. To accomplish this task, several aspects need to be considered. A crucial aspect at this stage is the expected effect size of the drug and the known variation of the primary endpoint measure, which together govern the power calculation and the sample size needed. As any treatment effect will need time to develop, time is also an important component: if the study is too short important effects or relevant but rare adverse events may be missed; if the study is too long patient retention may be difficult and dropouts may lead to missing data. A realistic estimate of the expected treatment effect on the primary endpoint and a sound power calculation are the mainstay of a successful study. Besides, there are numerous risk factors which may jeopardise the conduct and outcome of a study: 1) diagnostic imprecision and misclassification; 2) heterogeneity of the study population due to variations in disease severity or disease behaviour; and 3) adverse events and comorbidities. All of these may have unexpected effects on the primary endpoint or cause increased dropout rates, both of which may eventually weaken the statistical robustness of the study. Ideally, the study design balances all the beneficial effects and potential risks to allow a positive, statistically significant outcome of the study with appropriate sample size and duration. To accomplish this task, all clinical trial protocols define more or less rigorous inclusion and exclusion criteria. Inclusion criteria are designed to ensure that treatments are applied to the patient population most likely to benefit. In this context, they work as enrichment strategies to homogenise and optimise the study population, maximise effect size and minimise endpoint variation in both the active treatment and placebo arms, thus allowing detection of even small changes of the endpoint with statistical significance. Exclusion criteria also reduce heterogeneity of the study population but, in addition, minimise the risks of dropouts, which may jeopardise the statistical robustness of the study. Therefore, patients in whom a treatment is assumed to be unsafe or likely ineffective are excluded. On the other hand, both inclusion and exclusion criteria reduce access to the study for patients with the disease. This is a critical point, as excluding major parts of the population with the disease results in a study population that is no longer representative of all the patients with the disease. Consequently, once the study is positive, this will lead to a restricted approval of the drug by the authorities. Restricted approvals are a downside for both the patients who may not get a potentially beneficial treatment reimbursed, and for the pharmaceutical companies due to limited market access. From this aspect, an “all comers” strategy appears the most straightforward approach for all clinical trials (especially in phase III) and would also lead to broad approval of the drug in case of success. However, given the feared risk of failure with an “all comers” strategy, restrictive inclusion and exclusion criteria are prevalent in clinical trial protocols. Figure 1 shows the delicate balance between exclusive and inclusive trail strategies with effect size and side effects of the drug, statistics, costs and practicability as common denominators.