Brief Communication

Seeding trials: Marketing gimmick or credible scientific research

INTRODUCTION

The pharmaceutical sector has become extensively competitive over the years across the world and India is no exception. While the World Health Organization (WHO) recommends 433 'essential medicines' around 110,329 brands of registered pharmaceuticals, many of which are 'me-too' agents.[1,2] Competition in the industry fuels research and development, keeps prices of medicines in check and provides alternative therapeutic agents for the patients. However, in an overcrowded competitive market, enhancing or even sustaining sales volume and profit margins becomes increasingly difficult. Therefore, pharmaceutical companies often adopt aggressive and innovative marketing and positioning strategies aimed at influencing the prescribing habits of the physicians and try to usher them towards new medicines.[3,4]

While prescribing new drugs, physicians often try to balance a range of factors, such as potential benefits and risk, long-term effects, cost and range of therapeutic indications. For quick assessment of these factors relatively little information is available in public domain and physicians have little or no prior experience with the use of the drug in a new indication. Under such circumstances, prescribing may be more 'an act of faith' than a rational process. In order to 'educate' and familiarise the prescriber with the new drug or a new indication of an old drug, manufacturer(s) often adopt various techniques.[3] Prominent among them are detailing by professional sales representative, distribution of promotional literature and physician's sample, conducting programmes such as continuing medical education (CME) activities, symposia and conferences, etc.[3,5] Another lesser-known method of drug promotion is 'seeding trials' or 'marketing trials'.[6]

What are seeding trials?

Seeding trials are clinical studies designed by pharmaceutical companies with primary intention to promote the use of drugs that were recently approved or are under review by regulatory authorities.[6-8] Such trials have been described by Kesseler and colleagues as 'company-sponsored trials of approved drugs that appear to serve little or no scientific purpose". Many believe this as a marketing strategy in the guise of science. They are done to get physicians prescribe the new drug being marketed by the company rather than finding the safety and effectiveness of the drug.[6] The company promotes the new drug by sponsoring a clinical trial in which physicians participating as investigators are familiarised with the drug as they follow the trial protocol. It attempts to gratify the participating physicians by engaging them in the research team with the title of 'investigator'. This honorable and supposedly academic involvement with the pharmaceutical industry for the cause of advancing science is often perceived as qualification for a physician to become 'an opinion leader' among their colleagues.[9] While the apparent purpose of such a study is to test a scientific hypothesis, the true purpose is to 'seed' the habit of prescribing the new drug into the trial investigators.[8] The company puts its new product in the hands of physicians, hoping that the experience of treating patients with the study drug and the pleasant interaction with the company will translate into increased prescription of the drug in their routine practice.[7] Early experience of using a new drug during its clinical development strongly influences its future use by the physician.[10] Andersen *et al*. had checked the association between physician participation in a clinical trial of fixed-dose combination of formoterol and budesonide, an asthma drug, and the prescribing patterns of their practices in the 2 years following the trial. The control group comprised general practitioners who did not participate as investigators in the clinical trial. They found that conducting the trial led to a significant increase in the use of the trial sponsor's drug by the investigators in their own daily practice as compared with the control group.[11] Seeding trials are also employed to trigger a 'switch' of brands from a competitor product to the new drug, thereby increasing volume of sales.[8] Another possible objective of conducting such trials is to convert the investigators into brand ambassadors of the new drug and use their research experience as testimonial for promoting the drug.[6]

The key opinion leaders and the cascading effect

Opinion leaders are individuals who possess expertise, currency of knowledge and good interpersonal skills which enable them to communicate effectively with their peers and informally influence their attitude and behavior. A major marketing strategy in pharmaceutical companies involves influencing key opinion leaders (KOLs). Therefore, KOLs, who are well-known

physicians are identified by the sponsor during the course of such seeding trials and convinced about the benefits of the study drug. Besides prescribing the new drug, KOLs also serve as valuable channels for promoting the new drug during informal interactions with their colleagues and through presentations and discussions in various scientific forums.[12,13] The opinions and prescribing habits of senior physicians are sometimes imprudently followed by their students and staff. This may be due to 'role modelling' of the behavior and practices of the senior consultant by junior physicians.[14] It is likely that resident doctors will pick up the habit of prescribing the sponsor's new drug during the course of the trial and help in further driving up sales of the drug. Moreover, general practitioners and non-hospital-based specialists tend to follow what specialists from tertiary care or apex institutes prescribe and formally or informally communicate through CMEs, newsletters and consultations.[15,16]

The characteristics of a seeding trial

It is difficult to define the characteristics of a seeding trial. However, some broad aspects can be identified, which includes the following:[6-9,17,18]

(1) Lack of well-defined objective(s)
(2) Broad-based eligibility criteria
(3) The recruitment of investigators who are not experts or leading researchers but frequent prescribers of competing products in the same therapeutic class.
(4) Disproportionately high investigator's fee and payment on a per-patient scheme.
(5) Multiple investigators and multiple sites – with each site recruiting only a few participants.
(6) Inadequate statistical power and sample size.
(7) Open-label and non-comparative design without appropriate control group, with little or no trial monitoring.
(8) A trial with disease-oriented outcomes (i.e., surrogate markers) instead of clinical or patient-oriented outcomes.
(9) A trial not aimed at gaining regulatory approval (mostly post-marketing studies).
(10) A short-term trial for a chronic disease.
(11) Protocol development and trial coordination being done by the marketing division of a pharmaceutical company, instead of the medical or research and development division.
(12) A trial with an inordinately long delay between completion and publication.
(13) Provision of training and information package for interaction with media
(14) The marketing objectives of the trial are not described in the informed consent form.

Certain subtle characteristics of the new drug also make it a likely candidate for such clinical trials.

(1) The 'me-too' nature of the drug within an already crowded therapeutic class
(2) Potential for use in chronic disorders, especially lifestyle diseases like type 2 diabetes mellitus, hypertension, obesity and dyslipidemia
(3) New drugs that are disproportionally expensive compared with others in its class and which may, therefore, require special marketing strategies.

Can the intent of seeding trial be proved?

Seeding trials have been described in medical literature since the early 1990s.[19] However, documentary evidence regarding the intent behind such trials is available only for very few trials as a result of legal proceedings against pharmaceutical companies or because it was disclosed by physicians who refused to participate in such projects.[9,18] Some well-known seeding studies are STEPS (Study of Neurontin: Titration to Effectiveness and Profile of Safety) and ADVANTAGE trial (Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness).[7,20,21]

The STEPS study was a Phase IV uncontrolled, non-blinded trial, was designed to study the safety and tolerability of daily doses of Neurontin (gabapentin) and recruited 772 investigators to enrol, 2759 patients whose partial seizures were not completely controlled. It involved untrained investigators with little clinical trial experience. Patient follow-up was poor and data were not properly documented, but the overall findings suggested that the drug was safe and well tolerated by the patients. After the motive was detected, the company paid 430 million USD as settlement charges, after which there was 28% relative reduction in gabapentin market share.[22] However, it is still used off-label for various painful conditions including fibromyalgia, chronic low back pain and migraine, often as an alternative to opioid therapy as prescribers tend to continue patients on this drug rather than deprescribe it.[23]

The ADVANTAGE study was carried out to evaluate the tolerability of Vioxx (rofecoxib) in comparison to naproxen for treatment of osteoarthritis. It recruited 600 investigators to enrol 5,557 patients and started

in March 1999, approximately 2 months before the drug's US FDA approval. Data collection and analysis were carried out by marketing division of the sponsor rather than the investigators themselves. There was documentary evidence that the sponsor had designed this study only to familiarise the investigators, mostly primary care physicians, and generate sales of the drug once US FDA approval was obtained.[7] Vioxx became a blockbuster drug until it was voluntarily withdrawn by Merck in 2004, due to cardiovascular adverse events; much before the ADVANTAGE study's real motive was revealed.[24]

Adverse impact of seeding trials

Often, seeding trials are conducted just prior to marketing or as post-marketing trials without an appropriate control group. Stephens (2003) evaluated post-marketing surveillance studies and described the marketing angle of such studies.[17] Though some scientific data do get collected during such trials, their quality is not reliable and the scientific validity and utility are usually limited.[20] If such trial reports get published in peer-reviewed medical journals, they can create scientific confusion and controversies that may require clarifications at a later stage, and if they are rejected, they end up wasting editorial time.[10] Apart from scientific concerns, seeding trials should also be evaluated from an ethical point of view. The sponsoring company knowingly deceives the investigators about the real objectives of the study. Moreover, physicians are manipulated into prescribing and promoting the drug. The trial participants are also not informed about the true objective of the study in their informed consent documents. Sometimes, the protocol may be so designed that the trial participants are compelled to purchase the drug (sometimes at subsidised price) during the study period. Such trials do not yield sound scientific data but may lead to adverse events or sometimes even death of the participants. This was evident in the STEPS trial where 11 patients died and 73 more experienced serious adverse events.[21] Moreover, seeding trials can undermine trust in the clinical research enterprise, tarnish the noble image of the medical profession and lead to general mistrust of healthcare providers by society at large.[18,19]

How Institutional Ethics Committees should handle seeding trials?

Seeding trials are carefully strategised to impersonate as authentic clinical trials and escape the scrutiny of members of Institutional Review Board or Institutional Ethics Committee. To be able to identify such trials, members of IRBs/IECs should be able to read between the lines of submitted protocols and critically analyse the stated objectives. Some points to consider are listed in Table 1.

Status of seeding trial in India

In the early part of 2000s, India became the preferred destination of multi-national pharmaceutical companies to carry out the clinical trial. Not only are new drug being tested but several existing drugs and old abandoned drugs are also reinvestigated for new indications.[22] However, clinical research in India is constrained by the lack of trained investigators. In such a backdrop, conducting marketing trials in the guise of science would be relatively easy. Additionally, the use of fixed-dose combinations (FDC) in India is much higher than in other parts of the world and standards for their regulatory approval are not very stringent, which can indirectly be an incentive for carrying out poorly designed marketing studies. Though no objective assessment has been conducted so far in India to tag a trial as seeding, but the probability of such trial cannot be ruled out completely.

Table 1: Questions to be asked by ethics committee members

General
Is the medicine in question very expensive which otherwise patients would be reluctant to buy?
Is the medicine of the high-demand category where particularly the rich people would be tempted to buy, e.g., for osteoarthritis, psoriasis, neurological pain, cancer, obesity, anti-aging, osteoporosis
Is the drug developed for a commonly prevalent but non-serious disease, for which the public can be quickly motivated through trials? For example memory enhancers for children, vigor and vitality enhancing in young and middle aged, osteoporosis prevention medicine in elderly.
Are there some equally effective medicines in the market against which the company may wish to compete by using the trial data?
Trial specific
Is the trial trying to answer a trivial question or merely reaffirm an already answered question?
Are the objectives and endpoints of the study in synchrony with the stated research questions?
Are relatively inexperienced investigators involved in the trial?
Are there a disproportionally high number of general practitioners and private practitioners as investigators?
Are the investigators given any special incentives for reaching recruitment-related milestones, such as 'best physician awards' or 'free lunch' in any form?
Do the informed consent documents contain an unusually high claim of benefit (both direct and indirect) and low risk of the study medicine
Are the study participants required to purchase the study medications from the sponsor during the duration of the study?
Will the results of study likely to influence the prescribing pattern in primary and secondary care hospitals, through the generation of multiple KOLs?

CONCLUSION

A new drug/formulation developed with intense scientific efforts is ultimately crowned as a success if it benefits a large patient population, provides adequate relief from symptoms or disease progression and earns revenue for the manufacturer. However, when marketing and revenue generation disproportionately overrides science such as in seeding trials, it must be promptly identified and discouraged. Increased transparency from sponsors, increased vigilance by IRBS/IECs and increased scrutiny by investigators would prevent such unnecessary trials.

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Conflicts of interest

There are no conflicts of interest.

Biswa Mohan Padhy, Bikash Ranjan Meher

Department of Pharmacology, All Indian Institute of Medical Science, Bhubaneswar, Odisha, India

Address for correspondence:
Dr. Bikash Ranjan Meher,
Department of Pharmacology, All Indian Institute of Medical Science, Bhubaneswar, Odisha, India.
E-mail-pharm_bikash@aiimsbhubaneswar.edu.in

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