INTRODUCTION

The reason why this topic was selected was because of the current clinical trial related media coverage where it has been implied that CTs have caused many deaths. It was felt important to have an informed discussion with various participants in clinical research such as the sponsor, investigator and Ethics Committee member, so that one has different perspectives to mull over before deciding on what really is the truth behind such allegations. It begins with the question, why have trials that explore hard endpoints, where the new drug is evaluated based on its ability to prevent or reduce the risk of death or serious adverse events (SAEs)/morbidity in comparison to the current standard of care?

The world of pharmaceutical drug development has seen many drugs that for example, lower surrogate endpoints such as HbA1c or blood pressure (BP) very well; however, later were shown to increase morbidity and/or mortality or failed to reduce the hard endpoints significantly better than the current standard of care. Some of these drugs eventually had to be withdrawn. From a regulatory standpoint it therefore, became imperative to ask innovator or original research drug manufacturers to demonstrate that the investigational product is also able to reduce morbidity and/or mortality better than existing standard of care. To be able to show this one has to design what are called outcome trials where the endpoint is death or a major adverse cardiovascular event such as stroke, myocardial infarction, etc., Naturally, such trials are endpoint or event driven trials and accordingly patients at risk of such adverse events (AEs) are enrolled. In such trials, the event is to be expected and it is against such a backdrop that the new drug is tested.

In the world of diabetes, following the rosiglitazone controversy, the US Food and Drug Administration (FDA) in
December 2008 made it mandatory for innovator companies to conduct, within their anti-diabetic drug development program, a pre-specified, prospective, independently adjudicated, cardiovascular safety meta-analysis from an approval perspective, and even after approval they are asked to do large, long-term prospective cardiovascular (CV) outcomes trials powered for such events as the primary endpoint.

In India, such trials can garner a lot of media publicity and parliamentary standing committee scrutiny, which is why the Drugs Controller General of India’s (DCGI’s) office is a bit wary of approving such long-term prospective outcome trials. In fact, the DCGI’s office may not approve such 5-6 year trials at one go and often approves for 2 years, following which the company has to submit continuing safety data to get the approval extended for the full duration of the trial.

The other issue is the compensation guidelines, which were floated as a draft and have recently (Jan 30, 2013) been published as a gazette notification. Would every death or SAE in outcome trials be deemed compensable? Would AEs need to be doubly reported in such trials, as the DCGI’s office has asked? In developed markets outcome trials are the order of the day and do not encounter such regulatory questions. Nor is compensation an issue the way it has been made out to be in India. At the annual Indian society for clinical research (ISCR) conference, it was therefore, felt necessary to engage all stakeholders in a debate to thrash out issues from all perspectives. An new drug advisory committee (NDAC) member was also invited but could not make it and the next 4 pages outline these different perspectives.

**SPONSOR’S PERSPECTIVE**

Hard endpoint studies are clinical trials that measure categorical outcomes following therapeutic intervention in patients. Examples of hard endpoints include critical event endpoints such as an acute myocardial infarction or stroke, disease progression, duration of survival and mortality. In contrast, soft endpoint studies measure surrogate markers such as BP or cholesterol levels, disease severity, or quality of life. The value of hard endpoint studies lies in the fact that they measure the actual impact of treatment on disease outcomes, thus, directly validating the benefits of treatment. Thus, only hard endpoint studies can provide an estimate of the public health value of new treatments and their impact on national and global burden of disease.

However, hard endpoint studies are much more complicated and difficult to complete. Since they are designed to measure hard outcomes that are episodic and relatively infrequent during the course of a disease, they take longer to complete, making them more complex. Since they run longer and by definition involve patients that have suffered recognizable morbidity, they consume more resources both in terms of money and equipment/personnel. By definition again, patients in hard endpoint studies will suffer from at least one SAE during the course of the trial. It must be remembered that endpoint SAEs in hard endpoint studies are generally expected as a consequence of the progression of disease and as such, do not signify safety risk of treatment.

The importance of hard endpoint studies in regulatory decision-making has grown in recent decades. In the past regulatory authorities were inclined to accept surrogate endpoints, considering the difficulties of completing hard endpoint studies. However, several instances of contrarian experience has led regulators to exercise more caution. Trials that have been successful in reducing BP have not necessarily improved outcomes or survival in patients with hypertension, raising HDL cholesterol levels has not always resulted in less vascular disease, and trials with antiarrhythmic drugs have ended up with more deaths in the test group despite successful suppression of arrhythmia. Although, isolated changes in a surrogate endpoint may, indeed, be associated with favorable outcomes, pharmaceutical interventions invariably affect more than one set of variables that influence that outcome, and the ultimate effect is often unpredictable, making hard endpoint studies unavoidable. Surrogate and soft endpoint are still valuable for hypothesis testing, as secondary endpoints, and for follow-up studies probing the pharmacology of new drugs and comparing the effects of a variety of therapeutic options, but not as a tool to generate pivotal evidence of therapeutic value.

Hard endpoint studies are, therefore, the *sine qua non* of pharmacoeconomic evaluation and help define the ultimate place of a new intervention within the therapeutic armamentarium.

In conclusion, it would not be inappropriate to say that hard endpoint studies are the only true measure of the benefit-risk ratio and it is not surprising that they are emerging as the gold standard before products can be allowed access into the market at large.

**Dr. Shoibal Mukherjee, MD, DM**

Chief Medical Officer, VP Medical and Head Asia Medical Sciences Group, Quintiles Research Private Limited; Medical Director for Pfizer India from 1997 to 2006, Vice President, Medical Affairs and Clinical Research at Ranbaxy Laboratories from 2007 to 2008 and Senior Vice President, Clinical Development at GVK Biosciences; Founder member of ISCR.
INVESTIGATOR’S PERSPECTIVE

“The greatest deficiency of medical education throughout the twentieth century……was the failure to train learners properly for the clinical uncertainty, which led to the systematic overuse of tests, procedures, and treatments.” Kenneth Ludmerer, Time to Heal, 1999.

Hard endpoints are very important to the clinicians although, making a recommendation to a sick person in an era when several medications are available. Although, it is important that a drug is approved quickly based on intermediate or surrogate endpoints, all clinicians do wish that it will be effective, not harmful and is not withdrawn from the market at a later date due to safety or ineffective reasons.[1] Approving drugs based on intermediate endpoints is like declaring India the winner after Sachin Tendulkar has hit a century. We know that India has lost many matches after Sachin had scored a century. The Center for Drug/Biologies Evaluation and Research of the FDA in the US has published a guidance document for industry on clinical trial endpoints for the approval of cancer drugs and biologics.[2] Overall survival, disease or progression-free survival or time to progression, objective or complete response rate, and patient-reported outcomes from a quality of life or utility perspective is extremely important in those with the hard endpoints. Blinding can be difficult due to various reasons such as the side-effects. Blinded centralized review is generally needed in trials that use tumor progression as an endpoint. However, phase-III studies need hard endpoints.[1]

Clinicians donning the mantle of an investigator in the clinical trials are besieged by many issues. This include disease related ones such as cancer progression and complications arising from the disease itself, obtaining properly informed consent, blinding and un-blinding of toxic medications, placebo use, early closure of trials, providing the standard of care to those without financial support, reporting AE, SAE, and SUSAR to data safety monitoring board (DSMB), ensuring compensation, where indicated and justifiable, etc., Moreover, once the trial is over will patients who have responded to treatment continue to receive the treatment free of cost until disease progresses or until the drug cannot be tolerated? Large proportions of patients in India spend out of pocket for medical care and are often agreeable to participate in CTs for oncologic drugs, which they cannot afford otherwise. In many instances, the trial subjects do receive the effective drug for life. In some cases, the drug is even made available free of cost to those below the poverty line as part of patient access programs. Some get partial assistance where they pay for a few cycles after, which they get the drug free of cost for life. I have come across patients who get very good care for a long period while on CT much beyond what they would have ordinarily managed. For many diseases such as advanced cancer the course is downhill. Therefore, death is inevitable even when receiving the standard of care medication. Therefore, death is not caused by participating in a CT. Any good clinical practice (GCP) compliant CT trial always looks after the patient’s interest first and ensures that any potential for harm is minimized. The supportive care is so good that patients in CT almost always have better results even in the control arm compared to usual practice. Drug developments in cancer almost always are carried out in patients with metastatic disease in patients with very advanced cancer. Oncological trials are therefore, often associated with tumor progression that can be mistaken for lack of expected efficacy and cancer related complications can be mistaken for AE and therefore not deemed compensable.

In 1957, David Karnofsky wrote in the journal Radiology, “one of the difficult points to communicate, is that cancer is a continuous and evolving process with an orderly, and to some extent logical, picture of growth and change, rather than a series of unrelated medical crises such as the moment of recognition and diagnosis, the drama of the attempt at cure, and in many cases the frustration of inevitable dissolution.”[3] This statement is 100% true even today. All patients in a CT and their caregivers are explicitly informed about the end point—“death” or recurrence. It makes them extremely vulnerable to seek extreme remedies. They become apprehensive about being randomized to an inferior arm and can withdraw consent later on, or get lost to follow-up when the tumor progression occurs. The real language of the informed consent form is also important in a multi-linguistic country like India. Should the investigator or co-investigator also know the language of the patient? How does one know if the interpreter conveyed the right information to the subject? Ideally all informed consent process should be comprehended consent, overseen by an Ethics Committee member and this can prevent a patient accusing an investigator of not giving proper informed consent or perhaps the process video-recorded as suggested by the US-FDA while keeping the patient identity confidential.

Concealment of allocation in an RCT can be challenging as the desperate patients want to be randomized to the treatment arm. The principal investigator (PI) may also wish this for some of the patients. Interactive voice recording system has solved most concealment issues. Blinding is needed in studies with soft endpoints but is not very important in those with the hard endpoints. Blinding can be difficult due to various reasons such as the side-effects. Blinded centralized review is generally needed in trials that use tumor progression as an endpoint. However, the decision to continue the patients on the trial medications or stop the trial is, however, the treating clinicians prerogative. This can sometimes cause dichotomy.
The difficulties of placebo controlled trials are many. Almost all placebo trials include the use of the current standard of care for all subjects. Yet there is a fear of not being treated, especially when there is no toxicity or no tumor response. In such situations, the patients want to get into the treatment arm, and there is an urge to break the blind when an SAE occurs or when questioned by ethics committee (EC)/institutional review board (IRB) members. In positive trials, the un-blinding and cross over often come at a time when it is too little and too late.

In global multicenter trials the standards of care vary widely. In other words, standard of care is not standardized for trials and must be inclusive and pragmatic. As the base line mortality and morbidity can vary widely depending on whether patient is from low versus high volume hospitals, public versus private (economic status), teaching versus non-teaching, and Indian versus Western systems of medicine. Therefore, while enrolling patients from distant locations, where co-morbidity and AE are managed is a matter of great concern. AE reporting and safety management is also complicated. What is attributable to disease versus the investigational drug, versus the standard of care medications can result in unnecessary dose modification. Furthermore, there are too many forms to be filled out for different purposes and too many data clarification forms to be responded to.

Compensation during CT is another area of great concern for all the academic investigators I have spoken to. Several aspects of the new government notification are not recommended internationally. These clauses will incentivize patient participation in clinical trials for the sake of compensation, restrict the low budgeted investigator initiated and government funded trials, limit the potential for development of new treatments for the people of India by clinicians and researchers of India, and ultimately increase our dependence on imported new medications in the years to come. We have explained these in a recent publication.[4]

In summary, trials with hard endpoints are absolutely necessary for phase-III trials evaluating new medications for approval. The trials with the hard endpoints create several issues, particularly the downhill natural history of advanced cancer, the informed consent process for a fatal illness, the reporting and management of AE, and SAE, the variable morbidity and mortality caused by standard of care treatments depending on the health-care settings, and the new compensation guidelines pose several challenges to an investigator participating in clinical trials.

Mohandas K. Mallath
Senior Consultant, Department of Digestive Diseases,
Tata Medical Center, Kolkata, India.

REFERENCES
1. Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? Ann Intern Med 1996;125:605-13.
2. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), May 2007. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf. [Accessed on 2012 December 28].
3. Karmoński DA, Golbey RB, Pool JL. Preliminary studies on the natural history of lung cancer. Radiology 1957;69:477-88.
4. Divatia JV, Desai A, Pramesh CS, Mohandas KM, Gupta S, Badwe RA. Compensation guidelines for research related injury in India. J Assoc Physicians India 2012;60:53-5.

ETHICS COMMITTEE MEMBER’S PERSPECTIVE (REPORT PREPARED BY INDU NAMBIAR AND VIRAJ SUVARNA BASED ON PRESENTATION MADE BY DR. URMILA THATTE)

The following ethical issues come to mind: scientific design and conduct of the study, risks and benefits, selection of the study population and recruitment of research participants, inducements, financial benefits, and financial costs, protection of research participants’ privacy and confidentiality, informed consent process, community considerations, and safety reporting.

From a scientific perspective the following questions need to be addressed, viz., can the design produce the results being sought, that is, is it “good science?” Does it involve methods that are inherently unethical, and could its results be produced equally well by a design that exposed participants to less harm? And whether the results that the study could produce are worth the burden or risk to participants because they are better in scientific terms? The cardiac arrhythmia suppression trial (CAST) trials did bring out the above points very well. Encainide, flecainide, and moricizine successfully reduced the premature ventricular contractions, but led to more arrhythmia-related deaths. And both CAST and CAST II had to be terminated prematurely.

The Avastin (bevacizumab) case was another example. Later in the clinical development program, two additional clinical trials showed no effect on overall survival or quality of life. Adverse effects including severe hypertension and hemorrhagic stroke were seen and approval for breast cancer was revoked. From a risk to benefit ratio, the following issues need to be sorted out. Use of placebo, even when on top of existing standard of care, in the arm uncontrolled with existing standard of care, even if there is the provision of rescue medication. It depends on the individual trial. Hard end point studies may mean longer
exposure to possibly ineffective but risky medicine. Are there community/societal benefits? And what about the most vexatious concern, viz., post-trial access? Especially, when it is mainly poor patients who are included in trials but later may not be able to afford that care when the drug is either not marketed in the country where the trial took place (hence the allegation, “patients are being used as guinea pigs”) or marketed at an exorbitant price.

What constitutes undue inducement (financial benefits/costs)? What about consent to perform genetic tests on collected and stored tissue samples? Is it right to have a blanket consent? Or should it not be optional? What about consent in emergency situations? Data from the CRASH-2 (tranexamic acid in head injury) trial shows that a 1-h treatment delay (that occurs due to consenting procedures) reduces the proportion of patients who benefit from the trial treatment from 63% to 49%. Mandatory written informed consent results in avoidable mortality and probably morbidity in participants in the trial. Delay in starting treatment can obscure a real treatment benefit (if it is a time-critical treatment). “The lethal effects we have shown might have been found decades ago had the research ethics community accepted a responsibility to provide robust evidence that its prescriptions are likely to do more good than harm” Roberts Ian, et al. Effect of consent rituals on mortality in emergency care research. Lancet March 24, 2011. DOI: 10.1016/S0140-6736 (11) 60317-6. From a safety perspective, the bullet points remain viz., what is the end point? If death/SAE, should it be doubly reported as an SAE and as an endpoint? From a causality point of view won’t it always be considered related and if so won’t it always be compensable? However, is this the right way of looking at it from both a scientific and ethical perspective?

Urmila Thatte,

Professor and Head, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai. Member, Scientific Working Group (Clinical Research) CCRAS and Scientific Advisory committees as a Clinical Pharmacology expert of the ICMR, Member Secretary, FERC, Member, Working Group, Pharmacovigilance Program of India, Member of New Drug Approval Committees (Govt. of India).

How to cite this article: Suvarna V, Nambiar I, Mukherjee S, Mallath MK. Pharmacovigilance Symposium ISCR Annual Conference Jan 5, 2013: Safety aspects of hard endpoint or outcome trials. Perspect Clin Res 2013;4:148-52.

Source of Support: Nil. Conflict of Interest: None declared.