Critical Issues in the Conduct of Antihypertensive Clinical Trials

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Abstract

This paper reviews the critical issues in the conduct of anti-hypertension (anti-HT) clinical trials. International guidelines and current clinical and biostatical practices were reviewed for relevant clinical, design, end-point assessments and regulatory issues. The results are grouped mainly into ethical, protocol and assessment issues. Ethical issues arise as placebo-controlled trials (PCTs) for HT lowering agents in patients with moderate to severe HT are undertaken. Patients with organ damage due to hypertension should not be included in long term PCT. Active-control trials, however, are suitable for all randomized subsets of patients including men and women, and different ethnic and age groups. Severity subgroups must be studied separately with consideration to specific study design. Mortality and morbidity outcome studies are not required in anti-HT trials except when significant mortality and cardiovascular morbidity are suspected. Generally, changes in both systolic and blood pressures (BP) at the end of dosing interval from the baseline are compared between the active and control arms as the primary endpoint of anti-HT effect. Onset of the anti-HT effect can be studied as the secondary endpoint. For maintenance of efficacy, long term studies of ≥6 months need to be undertaken. Error-free measurement of BP is a serious issue as spontaneous changes in BP are large and active drug effect on diastolic BP is often small. Placebo-controlled short term studies (of ~12 weeks) for dose-response and titration are very useful. Safety studies must be very vigilant on hypotension, orthostatic hypotension and effects on heart. In dose-response studies, at least three doses in addition to placebo should be used to well characterize the benefits and side effects.

Keywords: Hypertension, good clinical practices, blood pressure, randomized clinical trials, endpoints

Introduction

The global burden of hypertension (HT) and co-morbid cardiovascular diseases (CVD) is becoming heavier than ever before with each passing year. It is estimated that by 2025 up to 1.58 billion adults worldwide will suffer from some complications of or from HT.[1] That makes one out of each three adults, on an average, will develop clinical HT or its co-morbidities or both. Currently the prevalence of HT varies around the world, with the lowest prevalence in rural India (3.4% in men and 6.8% in women)[2] and the highest prevalence in Poland (68.9% in men and 72.5% in women).[2] However, in fact the low prevalence rates, for example, as those cited for India do not necessarily mean a really low occurrence of the disease in this population. Even those who are diagnosed with HT, treatment is frequently inadequate. In any case regardless of the prevalence rate, large or small, HT and related diseases must be intervened for prevention, diagnosis and control.

On a global basis, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) provides to the clinicians and the researchers alike an evidence-based approach to the prevention and management of HT. According to latest JNC, i.e. JNC7, in patients older than 50 years of age, systolic blood pressure (SBP) of >140 mmHg is a more important CVD risk factor than diastolic BP (DBP).[3] However, beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg. In addition, those who are normotensive, they will have a 90 percent lifetime risk of developing hypertension at the age of fifty five.[3] When it comes to the measurement of BP in practice or in clinical trials, what is important is that the "true" BP with or without intervention is measured, representing the underlying pathology rather than just the pressure. Factors such as diurnal rhythm and the short-term variability can also be important contributors to the "true" BP that needs to be corrected in a clinical setup. A detailed discussion of the BP measurement and the problems associated with it is beyond the scope of this paper, however, there are some excellent review papers and the JNC7 Reference Card available that deal with the important aspects of HT clinical trials.[4-6]

Obesity, dyslipidemia (lower HDL levels), insulin resistance, diabetes mellitus (DM) are the disease conditions that often co-exist with HT. Perhaps physical inactivity and genetic co-factors are involved in these co-morbidities. Reduced physical activity is also a risk factor in coronary heart disease (CHD). Other heart conditions such as congestive heart failure (CHF) and fatal or non-

fatal myocardial infarctions (MI) and ventricular hypertrophy (VH) also cause elevated BP and BP lowering drugs have been found efficacious to different extents in such conditions.[7]

A number of studies have been conducted on prevalence of HT and co-existing diseases in India.[8-10] These studies have been carried out in different geographic areas and in urban as well as rural area populations and have examined the disease prevalence in both men and women, as well. Using the JNC criterion of systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg, these studies have estimated a prevalence rate of hypertension among urban population ranging from 1.24 % in 1949 to 36.4 % in 2003 and for rural people from 1.99 % in 1958 to 21.2 % in 1994[8-10], which is in contrast with the study on global data by Kearney et al. (2004).[2]

On one hand this enormous disease burden poses a serious public health challenge at a community level for prevention, detection and control of the disease. Needless to say that population based approaches are to be promulgated on a global scale wherein awareness and lifestyle modifications along with therapeutic interventions for control and maintenance will have to be placed as the key programs. On the other hand, expanded research is also required to be carried out for the discovery of new and appropriate anti-HT interventions. This direction in research ought to be inclusive of those which may even replace the first line of treatment, with superior safety and efficacy profiles. This paper is an attempt to review the important clinical and regulatory issues involving the higher phase clinical research of the discovery of new HT drugs.

Good clinical practices (GCP)

The ICH Good Clinical Practices (GCP) E6 guidelines is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. These guidelines are already harmonized among European Union (EU), Japan, Australia, Canada, the Nordic countries, the WHO and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities under these jurisdictions.[12] Essentially the GCP stands for the public assurance that the rights, autonomy and benevolence of trial subjects are protected, that the trial data are ethical, scientific and unbiased, and also that the documentation allows for a reconstruction of the whole study by regulatory or other authoritative representatives of the society. It also describes the solemn responsibilities of the Ethics Committee, investigators, sponsor, monitors and the quality assurance function. Table 1 provides the essential organization of the E6 guidelines issued by USFDA.[12]

Early and current hypertension trials

Randomized clinical trials of anti-HT drugs are mentioned in the literature that date back to late 1960's to early 1970's. These early trials were carried out in rather select populations (both high and low risk elderly patients), and were mainly interested in efficacy measurement of the anti-HT drugs in lowering BP relative to placebo or no treatment. The trials of 1980's focused on middle-aged hypertensive individuals and later on the elderly. These trials mainly investigated the efficacy of β-blockers and diuretics in reducing the systolic BP in these patients and subsequently diastolic BP.

These early efficacy trials did not address the effect of anti-HT agents in controlling serious co-morbidities like MI, CHD and CHF. Their compliance with GCP was also rather poor.[13] During the nineties, large randomized trials in a much broader patient population came in vogue and a great portion of these trials elucidated whether and whom to treat with different classes of anti-HT drugs. Continuing to date, these trials of ACEIs, β-blockers, ARBs and CCBs investigated for exact end-point goals such as reduction of a certain percent of risk of MIs in Grade II HT patients over 1 yr of treatment. The trials evaluated often superiority of end-point reduction by one agent over other as opposed to overall efficacy of one agent or the other. Reduction in the relative risk of mortality from primary and secondary outcome measures is one of the main objectives of the RCTs over last 5-7 years.

The reason for the outcome measurement shifting from BP to non-BP actions is that for some drugs BP lowering is an inadequate marker (surrogate) of health benefits in HT. Anti-HT drugs can have important non-BP actions that may alter the benefit of BP lowering. For example, many anti-HT drugs have shown consistent beneficial effects on long-term mortality and morbidity most clearly on stroke and less consistently on cardiovascular events, such as, low and high dose diuretics, reserpine, and ß - blockers, usually as part of combination therapy (FDA guideline).[14-15] While the sponsor has the main responsibility of the trial, the institutional review board ensures that a given trial will be conducted by ethical norms. Trial investigators and quality assurance have key roles in generating the essential efficacy and safety data and assuring scientific procedures.

Ethical Considerations

The ethical considerations in HT trials arise mainly on two accounts. Firstly, is it really ethical to put a BP-patient on a placebo arm in a RCT or there has to be an active control of some sort in all these trials? Very special populations who are either fragile or cannot make their own decision represent the other main concern for the HT trials.

Placebo control hypertension trials

Placebo controlled HT clinical trials have been found very useful especially when the efficacy of BP lowering is to be measured in a

RCT. They have also been found useful in the determination of the end points as a direct effect of therapeutic intervention. Despite availability of a standard and efficacious treatment, the use of placebo-controls in CTs can be considered ethical when withholding the effective treatment leads to no SAEs and patients are fully informed about available therapies and the consequences of delayed treatment[12]. As mentioned above, in case of the HT trials, placebo controlled efficacy studies are particularly helpful in thoroughly quantifying the effect of treatment. The hazard to patients can be minimized by exposing them to placebo for the least possible time and obtaining proper informed consent from them. In addition, particular attention should be paid to reduce the probability of CV events by excluding subjects with severe HT or major concomitant risk factors.

There are several good reasons why placebo-controls, when appropriate, are preferred to active controls. Firstly, placebo-controlled trials are sensitive in distinguishing an estimate of pure effectiveness of the treatment without any external reference. This kind of estimation, however, is not useful for equivalence, non-inferiority and superiority trials. In these later trails, either a clinically meaningful effect of the control has to be preserved or exceeded. In addition placebo controlled trials require a smaller sample size to attain statistical significance than does comparing the experimental therapy to another treatment. As a result, these trials are faster and less expensive than active control ones, exposing fewer subjects to the potential risks of the experimental treatment.[16]

Use of active controls in hypertension trials

Many major trials for anti-HT drugs that have been conducted in last ten years (ALLHAT,[17-18] INVEST,[19] LIFE,[20] LIFE-ISH[21] and RENAAL[22]) belong to the category of active control RCTs. Basically two types of studies have successfully used an active control. The first groups of studies are those in which preservation of a clinically meaningful efficacy and safety margin is essential (equivalence and non-inferiority trials, respectively). Examples are INVEST,[19] LIFE,[20] and LIFE-ISH[21] studies. In the second group of studies using an active control, the margin of clinically meaningful effect is to be exceeded as seen in superiority trials. The ALLHAT trial used chlorthalidone, a diuretic, as an active control standard treatment in order to see the superiority of amlodipine, lisinopril or doxazosin.[17-18] Usually active control RCTs are designed in anticipation of CV events in patients at high risk and where long-term effects of the new or experimental interventions are to be observed. These trials, consequently, require relatively a higher number of patients in order to achieve the required number of end points rapidly or at the earliest possible time for statistical analysis. Since the effect of experimental treatment separated both from those of active control and natural history with data often requiring appropriate baseline correction, data from these studies are rather complex to analyse.[23]

Both safety and logistical problems can arise from the use of an active control. Such a control can sometimes be expensive and produce SAEs including irreversible toxicities and deaths in participating patient-subjects. In addition, active control trials because of their long duration of experimentation can show cumulative CV toxicities. Such problems must be overcome either through study design (e.g., dose titration) or intervention of an appropriate, but not interfering with experimentation treatment. If these problems with active controls cannot be overcome at all, development of new products must be abandoned.[15-16]

Protocol Considerations

The trial patient population

For participation in RCTs for HT or its co-morbidities, any patient with a BP >120/80 mmHg especially with one additional risk factor such as BMI >25 is at risk of developing clinical HT may qualify for the trial. Patients who are of 55 yr of age or more are particularly risk prone. Fig.1give the lifetime residual risk of developing HT for men and women and getting an appropriate anti-HT treatment, respectively, for those who are of 55 yr of age or more. Currently the patient population studied with a new anti-HT includes a broad range of patients with HT and co-morbidities. For mild to moderate HT, however, only BP can be studied in a CT by measuring both diastolic and systolic BP over the study period. More severe HT is usually studied with relevant concomitant illness, e.g., CHD and DM. Care should be taken that the drugs they need would not interfere with the observations of effects of the study drug. For example, for patients with CHF, standard treatment requires use of one to several agents (ACE inhibitors) affecting BP that could have pharmacological actions similar to those of the study drug.[23]

Grading of HT together with TOD secondary to HT needs to be established accurately. Patients, for example, with BP >160/110 mmHg and DM cannot be included in a placebo-controlled trials. Such patients, however, can be included in active controlled trials with proper safety monitoring. Patients from relevant demographic subsets should be studied, including both men and women, racial/ethnic groups pertinent to the region, and both young and older patients. The very old or "fragile elderly", that is, patients >75 yr old, should be included. In general, all population subsets should be included in the same studies, rather than conducting studies in subgroups. This facilitates comparisons across subsets in the same environment. An exception would be severity of subgroups, where study designs could be different for different severities. Patients with secondary HT, isolated systolic HT, and HT during pregnancy, and children with HT should be studied separately, if specific indications for use in those populations are being sought.[23]

Geriatric ethics

Ethics of including any elderly patients in a placebo-control HT trial,

especially those who are more than 75 yr of age, should be seriously looked at and if necessary restricted. Such patients are likely to develop age dependent isolated systolic HT and measuring the efficacy of a new treatment through placebo-control could be rather tempting.

Elderly patients often exhibit reduced autonomy in not being able to decide for themselves on various issues in trial participation. Such dependence must be taken into consideration and every attempt made to give these patients a consent process which is non-coercive, impartial and gentle in nature. Many elderly patients lose their ability to read and write, therefore an impartial witness must always be present during the information giving and agreeing with the consent process.[23]

Pediatric ethics

Experimenting for clinical efficacy or end-point in children poses a multitude of trial management or ethical challenges. Should there be pediatric studies at all or there should be a way of calculating posology for giving indications from relevant studies carried out in adult patients was the initial dilemma. However, with the Food and Drug Modernization Act 1997 conducting clinical studies in pediatric population has become more guided process than before.[24] It is anticipated that this development will benefit the children with HT and co-morbidities by increasing the understanding of the efficacy and safety of anti-HT agents. The designing of these trails are ethically questionable as for placebo controls because their inclusion practice for anti-HT trials in adults led to well-known adverse consequences of untreated HT. This is a critical issue in pediatric HT, as HT children have either secondary forms of HT or HT-induced TOD which increases the risk of harm during exposure to placebo. Therefore, a strict set of regulation for the use of placebos in pediatrics anti-HT trials has been proposed with strong emphasis to protect the vulnerable patient population.[25]

Randomized clinical trials of antihypertensive agents

All recent trials, since 1990's, for the assessment of efficacy and safety of anti-HT drugs have been designed and conducted as randomized, blinded trials.[18-22] Such trials are not only free of experimental bias, but they are also balanced in all important aspects of the study and differ only in the intervention that the experimental and the control groups receive. As discussed further in the following section, many big trials, such as INVEST and ALLHAT are designed as prospective, randomized, open, blinded-end point evaluation (PROBE) investigations in thousands of patients in multiple countries. In some studies, there is also an emphasis on the determination of the reduction of mortality and/or CV morbidity by the experimental treatments rather than measuring just the BP lowering effects.[26-27] Well-designed and well-conducted RCTs have been able to estimate such complex end-points with a great deal of success.

Study design and randomization

Most long term HT trials are designed today as prospective, randomized, open-label, blinded endpoint (PROBE) studies. Such studies are aimed at comparing a treatment regimen of newer anti-HT drugs (e.g., a CCB) with a traditional regimen (β-blocker and/or a diuretic), like prevention of CHD. The study basically consists of two arms, that is, control and experimental arms, in which appropriate number of patients are entered following a randomization scheme. Since the control arm in such studies consist of receiving an active drug which is often one of the standard first line treatments, the trial is often dubbed as an "active control trial", as mentioned above several times. A schematic representation of a two-arm randomized trial is presented in Fig. 1. The total number of patients (sample size) and those in each arm are calculated carefully such that a clinically meaningful effect size can be differentiated between the average outcome measurements for the two arms with adequate statistical power (usually 80%) and significance (usually two-sided 5%). Both the power and level of significance are prospectively defined and finalized in the detailed protocol before the trial begins. The final sample size includes considerations of drop out patients and all interim analyses (IA).[28]

The RCTs for HT and co-morbidities are usually large (few thousand patients) multi-centre studies.[26-27] Open label refers to a non-concealment of both the active control and experimental drugs to the patients and investigators in that they can figure out the difference in physical and organoleptic properties between the two. Sometimes there could also be a difference in the route of the two administrations. The investigator or the expert who measures the endpoint, however, is blinded to the randomization codes and allocations to all patients, such that no bias is introduced in the assessment of the endpoint. If dosage titration for the experimental arm is required, the same principle of endpoint blinding should be applied.[28]

Although there may be many sub-varieties, essentially there are three basic ways to generate randomization scheme for an RCT. The first approach can be called "simple randomization", which is equivalent to tossing a coin for each subject that enters a trial. The heads get the experimental treatment while the tails receive the placebo. A computerized or tabulated random number generator is generally used. It is simple and easy to implement and treatment assignment is completely unpredictable. The second approach to randomization, called the "block randomization" is very popular and balanced within each block. For a trial of n treatments, the total number patients are divided into m blocks of size 2n. Then, each of the m blocks is randomized such that n patients are allocated to each of the treatments. One can then choose the blocks randomly. The INVEST[19] study followed this scheme of

block randomization. Yet a third approach to randomization involves "stratified blocks". Since a trial may not be considered valid if it is not well balanced across prognostic factors, stratification of patients is done to produce comparable groups with regard to certain characteristics (e.g., gender, age, race, disease severity). This approach produces valid statistical tests in all stratified subgroups (e.g., high risk subgroups in ALLHAT trial).[17-18]

Whatever the mode of randomization is, it is ensured that the pattern of assignment of control or experimental drug within a group of patients cannot be guessed at any point. It is recommended that the statistician who generated the randomization codes does not get involved in the IA or the final analysis of experimental data.[23]

Other study designs can be used in HT trials as long as they are scientifically valid and manageable. Placebo controls have been described elsewhere in this article. True double-blinding of patients as well as the investigators is very difficult to achieve as the regimens in the two arms differ on a number of noticeable properties.[23]

Usually studies are designed for observation and analysis of the primary outcome on which the sample size calculation is also based. Secondary outcomes, however, can also be validly analyzed if the primary outcome difference is not statistically significant provided that they were declared *a priori* and are clinically important. Another condition for the valid use of secondary outcomes in efficacy or endpoint estimation is that the method to capture outcomes was the same in each treatment groups and the data are unbiased (randomized). In addition, if the outcomes for secondary endpoints such as heart failure (HF) and CVD are still compelling even after considering the number of comparisons made then the conclusion based on these outcomes is valid.

Inclusion exclusion criteria for entry into study

Following any standard inclusion and exclusion criteria may prove too restrictive or too liberal in a HT clinical study. Inclusion should be based on three basic scientific questions, viz., a) what is the primary objective of the study? b) which clinical symptoms, tests and physical parameters would represent the true patient population? and c) which clinical symptoms, tests and physical parameters will distinguish the outcome from baseline as well as from the control with sensitivity and accuracy? Similarly, the exclusion of all those patients who are likely either refractory to the experimental regimen or marginally meet the true and desirable patient criteria is based on having an experimental sample who will provide for the estimation of a clear and sharp effect size.

The rationale of inclusion and exclusion criteria for a large, long-term RCT for a new anti-HT agent (see Table 2) can be exemplified as follows. Say, the primary endpoint for this trial (comparing a new ARB with an existing combination of β-blocker and diuretic) is reduction of fatal CHD and non-fatal MI. Both men and women of age 55 yr or more with systolic and/or diastolic BP 140/90 mm Hg but 180/110 mm Hg (treated before or untreated) at two visits with no washout period leading to randomization can be recruited.[3] Addition of one or more risk factor will give a representative sample of patients who are most likely to be benefited from the treatments and also a sensitive and accurate baseline to which the post-study primary outcome between the two arms can be compared and contrasted. Therefore, patients with at least one additional risk factor should be recruited for this trial and randomly assigned to one of the arms.

Conduct and Analysis of the Study

Study conduct, data capture, monitoring and auditing

A meticulous, accurate, ethically approved protocol must be followed for each study. All contentions about the protocol must be resolved jointly by the sponsor, investigators and experts. Once the protocol is finalized, no change should be encouraged unless it is absolutely necessary. Just before initiating the trial, a comprehensive meeting of all the stakeholders, especially with all the principal investigators (PIs) and their associates' results in a higher co-operation during the trial. Such meetings can be had during the ongoing trial as well with proper care being taken that no data analysis is attempted in these meetings.

The main body of data will be captured on manual or electronic case report forms (CRFs). Either method of the capture needs to be validated for their performance. All source data (physicians' evaluation sheets, original test reports) need to be preserved along with the CRFs. Proactively, this is achieved through data monitoring and correctively by auditing. One has to make sure that the CRFs are filled properly, source data and trial master files (TMF) are maintained and are error free and the conduct is GCP compliant. More advanced and formal data monitoring arrangements such as the data safety and monitoring board (DSMB) often assume the highest authoritative positions in looking into interim data, meaningfulness and proper conduct of the study and safety of the participating patients. A recent guidance from USFDA has spelled out the role and responsibilities of such a data monitoring board.[28]

Data auditing for quality, GCP and proper conduct including validation of employed methodologies in the trial is a post hoc process as contrasted with the proactive monitoring functions. Usually the data auditors are highly trained in individuals who examine a given portion of the trial data and certain processes therein against a set of pre-planned criteria. A private audit is often carried out for a pivotal trial prior to the possibility or actual inspection by an FDA.

Data analysis and results interpretation

Only cleaned (accurate, error free and formatted) and locked

Medical evaluation of data may look into raw and unclean data as well. Confounding factors not only give important clues about the ongoing trials but also for the future trials and trial guidelines. Perhaps this is one of the reasons why the regulatory agencies ask for analyzing the trial data both as "intent to treat" and "per protocol" analyses. Intent to treat methodology includes all data from all patients who have been randomized irrespective of whether they completed the study or not. Per protocol analysis on the other hand looks at the conclusions from the data of all those patients who have completed the study duration and fulfilled all other criteria according to the protocol. Sometimes the two analyses result in two different conclusions such as the intent to treat reveals that the new therapy is not effective whereas the per protocol analysis finds it effective. The reason for such dichotomous conclusions must be sought out as in principle both these methods of analysis of clinical trial data are supposed to yield consistent conclusions.[27]

A detailed discussion of the statistical methods employed in analyzing HT trial data is beyond the scope of this paper. However, in general, in efficacy trials, comparison of the mean blood BP lowering can be done by conventional tests of hypothesis, for example, t-test to compare the relative efficacy of two treatments. On the other hand, in more complex, long-term end-point trials aiming to examine efficacy as well as reduction of morbidity and mortality, comparison of relative risks or hazards of two treatments is made. In these latter studies analyses of time to event data and Cox regression are often employed to estimate the relative benefits of treatments.[27]

Evaluation of safety

All anti-HT agents have adverse effects on various organs and systems and can also exacerbate a pre-existing damage when used chronically. Since tremendous volume of safety data is generated in the HT-RCTs, maintenance of a database and proper evaluation of the safety profile is required not only during the trial but also at regular intervals post-approval. ICH E1 guidance suggests that a database of about 1500 patients (300–600 for 6 months, 100 for 1 yr) is usually sufficient for chronically administered drugs. Even larger databases may be required for large trials with commitments of long follow-up periods before and after the approval of the trial drug. [3,27]

Attention must be given to the BP related adverse events in all HT trials such as excessive hypotension, orthostatic hypotension and rebound phenomena. Depending on the particular drug and other observations, studies of effects on heart rhythm or cardiac conduction, coronary steal effects, effects on risk factors for cardiovascular disease (e.g., blood glucose, lipids), and further deteriorating effects on TOD can also be carried out.[23]
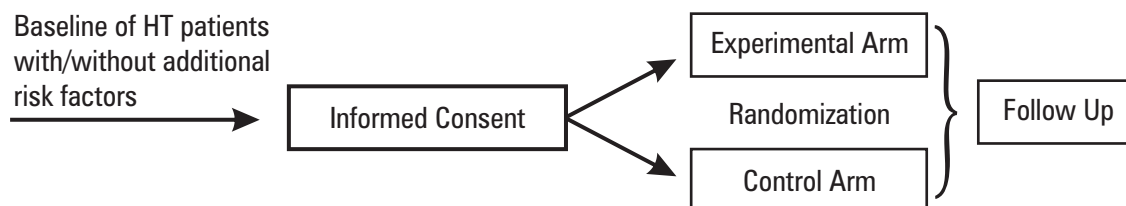

Fig. 1: Schematic representation of a two-arm randomized clinical trial of new and existing anti-HT treatments in HT patients with one or more additional risk factors

Table 1. Roles and responsibilities of different important functions in randomized clinical trials as described in the ICH GCP guidelines[12]

Stakeholders and other functions	Roles and responsibilities
Sponsor	Securing agreement with different parties
	Overall conduction of the trial, handling and verification of data, conducting statistical analysis and preparation of trial report
	Designating medical personnel to advise on trial related questions
	Selecting investigator
	Providing insurance or should indemnify the investigator

Stakeholders and other functions	Roles and responsibilities
	Documenting financial aspects of the trial should be in an agreement
	Submitting application to appropriate authority for review, acceptance, and/or permission to begin the trial
	Supplying the investigator with the investigational product
	Defining, establishing, and allocating all trial related duties and functions
Quality assurance	Written SOPs to implement and maintain quality assurance (QA) and quality control (QC)
	Ensuring that data are generated, documented (recorded), and reported in compliance with protocol and GCP
	Securing agreements to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by domestic and foreign regulatory authorities
	Applying QC to each stage of data handling to ensure that all data are reliable and have been processed correctly
Investigator	Should be thoroughly familiar with the appropriate use of the investigational products (IP), as described in the protocol
	Complying with GCP and applicable regulatory requirement
	Responsible for all trial related medical decision
	Should have available time for conducting the proper CT
	Taking responsibilities for all trial related medical decision
	Conducting the trial in compliance with the protocol
	Responsibility for IP(s) accountability at the trial site(s)
	Obtaining and documenting informed consent
	Ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the case record forms (CRF)
	Reporting serious adverse events (SAE) immediately to the sponsor
Institutional	Safeguarding the rights, safety, and well-being of all trial subjects
Review Board	Reviewing a proposed clinical trial within a reasonable time and documenting its views in writing, clearly identifying the trial
	Conducting continuous review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year
	Ensuring that information regarding payment to subjects, is set forth in the written informed consent form

Table 2. Usual inclusion/exclusion criteria for hypertension randomized CT

Sl. No.	Inclusion Criteria	Exclusion Criteria
1.	Age/sex: men and women aged > 55 yr	Age/sex: men and women aged ≤ 55 yr
2.	BP eligibility: Untreated systolic and/or diastolic hypertension (140/90 mm Hg but 180/110 mm Hg at two visits) No washout period	MI, stroke, or angina within 6 months
3.	At least one of the following risk factors: Type 2 diabetes mellitus (DM) HDL cholesterol < 35 mg/dL on any 2 or more determinations in past 5 yr	Symptomatic CHF or ejection fraction < 35 per cent
4.	Left ventricular hypertrophy (past 2 yr) ECG, or echo (septum + posterior wall thickness 25 mm)	Known renal insufficiency - creatinine 2 mg/dL
5.	Current cigarette smoking	Requiring diuretics, CCB, ACEI, or ?-blockers for reasons other than hypertension

Conclusion

This article deals with most of the compliance and assessment principle that guide the conduct and conclusion of a meaningful HT trial.   By no means can this replace the blue print of medical documents, SOPs, expertise and organization that are required for a successful trial.   Each trial is as meaningful as the number of scientific questions it answers and paves the direction of future trials in that field.   Compliance to GCP opens up the data for correct interpretation.   Any neglect toward this end of abiding by the GCP principles can raise a slew of critical questions eventually rendering the entire data to be uninteresting or a suspect.   Principles of study design and analysis mentioned in this article can give the trialists an advantage of a well designed study providing the crucial evidence of safety and efficacy of the agent under testing.

Acknowledgment

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