

Clinical Drug Trials: Practical Problems of Phase III

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Abstract

Introduction: Phase III randomised clinical trials provide the highest level of evidence to support the superior effectiveness of a new drug or therapy. The main practical problems encountered in the initiation, design, conduct and completion of both investigator-initiated and sponsor-initiated phase III clinical drug trials will be reviewed. **Methods:** A Medline search of clinical drug trials conducted in Singapore as well as journal articles highlighting important methodological considerations and practical problems encountered in phase III clinical trials was performed. **Results:** Several phase III randomised clinical trials have been conducted in Singapore which include the investigation of interventions that include tramadol, estradiol patch and colloidal bismuth subcitrate. The main problems encountered in phase III clinical drug trials include difficulties with recruitment of subjects for the study, proper filing of case report forms, special problems in children and the elderly, adequate compensation for adverse events and the adequate archival of documents of the completion of trials. In investigator-initiated trials, careful attention should be given to identifying a suitable study question, choice of study design, sample size calculations and data analysis. In sponsor-initiated trials, a good working relationship with the sponsor is essential and publication terms should be spelt from the onset of the trial. **Conclusions:** Well-planned clinical trials led by a team of competent investigators are essential for the conduct of rigorous sponsor-initiated and investigator-initiated clinical trials.

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Key words: Consent, Evidence, Randomisation, Sample size, Singapore

Introduction

There has been a rapid increase in clinical trial activity in Singapore and other parts of Asia. Randomised clinical trials are the “gold standard” in study design, which enable the question of efficacy of different treatments or managements to be effectively compared. However, this result can only be acceptable if data collected are reliable and accurate, hence the need for rigorous studies.^{1,2} Clinical trials may be classified into phase I and II trials whereby preliminary testing of the drug is conducted for safety and efficacy. Phase III clinical trials are designed to test the efficacy of one form of management (be it drug treatment, surgery or screening) or versus a control (placebo or standard treatment) in a statistically large enough group of subjects, and phase IV trials which are designed as post-marketing surveillance for the side-effects and toxicity of a new drug.³

Phase III trials represent the most rigorous form of testing that provides the highest level of evidence that one form of therapy or management is superior to placebo or standard treatment. Examples of phase III trials conducted

in Singapore include the evaluation of drugs, surgical methods, health screening methods and health promotion exercises. Drugs that have been evaluated include enoxaparin prophylaxis for patients undergoing major colorectal surgery, cimetidine for duodenal ulcers and tramadol as pain relief for pregnant women in labour (Table I).⁴⁻¹³ Table I summarises several published randomised clinical trials conducted in Singapore whereby the majority used simple randomisation techniques. None of the trials in Table I were factorial or cross-over trials.

Phase III clinical drug trials may be investigator-initiated or sponsor-initiated. In investigator-initiated trials, the motivation for conducting the study is usually academic, in other words, a desire to improve therapy or management of disease. In a sponsor-initiated trial, the motivation is to obtain sufficient data to show that the new treatment is effective and safe, and a drug (or device) may be registered with regulatory authorities. The clinician works with a sponsoring agency that would have already formulated the trial protocol, usually to be performed in a multi-centre setting (to optimise recruitment). Whilst the motivations

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TABLE I: SOME EXAMPLES OF RANDOMIZED CONTROLLED TRIALS DONE IN SINGAPORE

Author (year)	Sample size	Randomisation (simple, stratified, block)	Placebo ?	Cross-over trial?	Factorial design?	Conclusion
Ho et al ⁴ (1999)	320	Simple randomisation	?	No	No	Enoxaparin prophylaxis is effective in patients undergoing major colorectal surgery
Khalil et al ⁵ (1998)	16	Simple randomisation	Yes	No	No	Fibre-containing enteral formulae do not reduce the incidence of diarrhoea in tube-fed patients
Viegas et al ⁶ (1993)	90	Simple randomisation	No	No	No	Tramadol was as effective as pethidine for pain relief for pregnant women in labour
McCarthy et al ⁷ (1992)	21	Simple randomisation	No	No	No	A new 50 micrograms estradiol patch was found to be as effective for estrogen replacement therapy
Kang et al ⁸ (1990)	282	Simple randomisation	No	No	No	Low-dose cimetidine treatment is less effective than standard doses in acute duodenal ulcer patients
Ratnam et al ⁹ (1990)	22	Simple randomisation	No	No	No	High-dose prednisolone was not found to be more effective than low-dose prednisolone in the prevention of relapse in patients with pemphigus
Kang et al ¹⁰ (1990)	73	Simple randomisation	Yes	No	No	Colloidal bismuth subcitrate benefited non-ulcer dyspepsia patients with gastritis but not those without gastritis
Singapore Tuberculosis Service ¹¹ (1991)	310	Simple randomisation	No	No	No	No evidence of therapeutic benefit of continuing streptomycin beyond 1 month or from adding streptomycin to HRZ (isoniazide, rifampin, pyrazinamide)
Woo ¹² et al (1990)	27	Simple randomisation	No	No	No	Combination regime of cyclophosphamide, dipyridamole and warfarin reduced proteinuria in patients with IgA nephritis
Koetsawang et al ¹³ (1980)	925	Simple randomisation	No	No	No	No significant difference in contraceptive efficacy between “natural estrogens” containing ethinyl estradiol

for phase III trials are different, the mechanisms are virtually identical. However, sponsoring agencies, such as pharmaceutical companies, have far more experience, expertise and resources to ensure that protocols are rigorous, complete data are captured and compliance with the protocol and Good Clinical Practice (GCP) are achieved, so that subsequent analysis can be performed. Investigator-initiated trials seldom achieve this degree of quality for the opposite reasons that sponsored studies can do so.

This paper covers the main practical problems from the initiation to the conclusion of phase III clinical trials. The advantages and limitations of special “cross-over” or “factorial” study designs will also be outlined.

Special Problems of Investigator-initiated Trials

a. Identifying the Research Question

Identification of such problems usually evolve around the lack of evidence for decisions that impact on patient's well-being and healthcare management, and may involve the full spectrum of illnesses from treatment of skin warts to optimal therapy of septic shock. The desired answer to

these questions in a new clinical trial usually is determined by the clinician, based on either absence of substantial data on the subject or costly treatments of unproven benefit. It should be pointed out that treatments that appear obvious and physiologically sound but unproven in clinical trial are important hypotheses to test out. An example of this is the use of anti-arrhythmic prophylaxis following myocardial infarction. It was not until robust clinical trials were performed that these agents were found to cause more deaths than the placebo.¹⁴

b. Literature Search

Once the question has been identified, in-depth research may be conducted with a comprehensive literature review based on a Medline search, Cochrane review methodology database or other databases, and hand searching of journals to evaluate the latest information on the evidence for the treatment(s) and the desired health outcomes of interest.¹⁵ In addition, a review of abstracts presented at major relevant local and international conferences as well as discussions with other research leaders in the field may be helpful. Questions that the investigator may ask include “Is anyone

else already doing this?” and “Or has this already been done?”.

c. Study Objectives

Once the question posed has been defined, the study objectives are easier to formulate.¹⁶ These are structured around the parameters of efficacy and are often called endpoints (primary or secondary).¹⁷ For example, a study of the risk factors for coronary heart disease may use acute myocardial infarction or coronary heart disease deaths as primary endpoints, and thickened carotid intima on Doppler ultrasound as a secondary endpoint.

d. Trial Design

The simplest design is a two-arm randomised placebo-controlled trial. Deviations from this create problems from the viewpoint of analysis and study size, and are not usually recommended. Appropriate randomisation methods are required, not methods such as coin-flipping.^{18,19} In double-blind studies, it is important for the investigator and patient to maintain the blind.¹⁹

e. Special Trial Designs—Factorial and Cross-over Designs

Special factorial designs allow us to study more than one new treatment as well as the joint effects of the new treatments. The simplest factorial design is the 2 × 2 complete balanced factorial design which has two treatments (A and B) and four different arms (A and B, A but not B, B but not A, neither A nor B).²⁰

In cross-over trials, patients switch or cross-over from one form of treatment to another at different times of the trial. The patients are randomly assigned to groups I and II whereby the patients in group I are assigned the treatments in the order A, B and patients in group II are assigned the treatments in the order B, A.^{21,22} The length of treatment under A and B are similar and there may be a wash-out period during the “switch over” phase where the patients in

both groups I and II are not given any treatment. An example of an on-going cross-over trial is the study with two arms 1% cyclopentolate followed by 1% tropicamide and 1% tropicamide followed by 1% cyclopentolate whereby the effectiveness of the 2 drugs in paralysing accommodation is studied.²³

f. Study Sample Size Calculations

Trial sizes of 50 or 100 patients are often seen in grant applications and raise suspicions by reviewers that insufficient effort has been put into this area. It would be woeful to spend 3 years conducting a trial to find that the study size was inadequate to answer the question posed, not to mention a waste of finances. Sample size calculations depend on the number of test treatments, the outcome measure, anticipated length of follow up and anticipated non-compliance rate (Table II).

g. Data Analysis

It is not wise to solely depend on hypothesis testing and *P* values as simple descriptive analysis is just as important.²⁴ A simple description of the proportions or means of the outcome variable and baseline variables in the different treatment groups would be useful. The outcome variable may be nominal (outcome experienced versus no outcome experienced) or interval-ratio. One of the simplest data analyses is to compare the proportion of patients who have experienced the outcome of interest (nominal outcome) in the control group and the treatment group. Statistical evaluation of the difference in proportions may be performed using Fisher's exact test or chi-square test. Multivariate logistic regression analysis may be performed to adjust for several confounders simultaneously. Survival analysis with life-table estimations and Cox proportional hazard modelling are statistical tools that may be used to take into account varying follow-up times.

h. “Intention-to-treat” versus “Treatment received” Analysis

In reality, not all patients enrolled in a clinical trial comply with treatment.²⁵ “Intention-to-treat” (ITT) is a principle whereby the patients in the clinical trial will be analysed according to the treatment group they were assigned, regardless of whether they actually received the treatment they were assigned. Many researchers feel that “intention-to-treat” should be the first line of data analysis as the protection of the randomisation code is very important and selection bias may be avoided. If there are many non-compliers and “cross-overs” from one group to another, the risk estimate will tend towards the null but will not be larger.²⁶

“Treatment received” (TR) is the principle in which patients are analysed according to the actual treatment received, which may be very different from the original

TABLE II: AN EXAMPLE OF AN EQUATION TO CALCULATE SAMPLE SIZE IN A RANDOMISED CLINICAL TRIAL

$$N_c = \{Z_\alpha \sqrt{(2PQ)} + Z_\beta \sqrt{(P_c Q_c + P_t Q_t)}\} / \Delta$$

whereby N_c is the required sample size for the control group

α is the probability of Type I error

β is the probability of Type II error

P_c is the event rate (expressed as proportion) for the outcome of interest in the control group

$Q_c = 1 - P_c$, P_t is the event rate (expressed as proportion) for the outcome of interest in the treatment group

$Q_t = 1 - P_t$

$\Delta = P_c - P_t$

$N = (r+1) N_c$, whereby N is the total sample size for all the groups.

randomisation assignment if there are a large number of non-compliers with the assigned treatment. However, treatment received analysis may give rise to spurious results caused by outcome factors that influence non-compliance in both arms. Furthermore, the randomisation code is broken and the sample size may be smaller. If there is non-compliance, the best approach would be to analyse the clinical trial by both “ITT” and “per protocol” analysis. A clinically meaningful result is more likely if the “ITT” and “per protocol” analyses yield similar findings.

Specific Issues Involved in Sponsor-initiated Trials

There are many reasons why clinicians choose to participate in such trials. Often there is a desire to determine whether the new treatment is successful. Publication is often another reason for such participation. Here the issues are quite different to those of investigator-initiated trials. Firstly, the data belong to the sponsor company, not to the investigator and there may be a problem if the trial results prove poor and the sponsor does not want publication of the results, especially if this is contrary to the investigator's intentions.²⁷ Secondly, the sponsor may not spell out the publication terms because they do not want to antagonise key investigators. However, GCP requires that publication policy must be settled before the start of the study so there are no disputes later. While one expects trial objectives and design to be well constructed, investigators should really look at this closely. There is a tendency for sponsors to try and squeeze in as many objectives as possible into a single trial and run the jeopardy of being unable to answer the question adequately. In a recent study of lamivudine for treatment of hepatitis B in Asia, the initial study comprised a three-arm design of placebo, 25 mg and 100 mg. Unfortunately, the follow-on study protocol required re-randomisation and patients were put on open-labelled drug if HBV DNA was detectable. Later analysis of the trial proved difficult as the 358 patients were then split into 7 arms from the initial 3 arms.²⁸

Investigators need to be aware of dubious study designs and can feedback to the sponsor during the forum for such discussions—the first investigator meeting. The investigator also needs to obtain the assurance that the sponsor will provide free drugs to the study subjects (including subjects taking placebo) should the drug be successful, until licensing. Pharmaceutical companies may not want to provide this, but not only is it morally important, but adds credibility that they do in fact wish to assist patients with the disorder. The subjects should receive compensation in the form of paid medical treatment, hospital expenses or reimbursement.

Singapore GCP (Good Clinical Practice) Guidelines

All clinical trials must conform to the Declaration of

Helsinki. The conduct of clinical trials in Singapore is regulated by the Medicines Act 1975 and the Medicines (Clinical Trials) (Amendment) Regulations August, 1998. The Singapore GCP guidelines were launched on 1 July 1999.²⁹ The guidelines were adapted from the International Conference on Harmonization (ICH) Guideline for GCP. The GCP guidelines in Singapore set acceptable standards by which clinical trials are designed, performed, monitored, analysed and reported. The guidelines set an assurance that the well-being and safety of the subjects are protected. In addition, the guidelines provide a uniform basis to ensure that the studies are carried out to uniform and the highest standards. Approval must be obtained from the Ethics Committee of the participating hospital or institution before a trial may commence. In addition, a certificate to conduct the clinical trial (CTC) has to be issued by the Ministry of Health.

There may be a delay in the commencement of a trial if incomplete or inappropriate submissions are made to the Ethics Committee. The submission to the Ethics Committee should include the protocol that addresses any possible ethical considerations in the trial such as informed consent, the safety of the proposed new treatment, and the appropriateness of the use of placebo. The submission should include a copy of the proposed consent form. The common mistakes in submission to the Ethics Committee are outlined in Table III. Delay may also occur if incomplete protocols are submitted to the National Medical Research Council for investigator-initiated trials.

Clinical Trial Study Team

The minimal clinical study team involves a single centre. Here, the principal investigator, co-investigators and the study coordinator are all that is needed to carry out the logistics of the trial. Assistance from a biostatistician is essential. If there is a considerable amount of data, then a specific data manager is required. Once a trial becomes multi-centre, or involves many subjects, the size of the

TABLE III: COMMON MISTAKES BY INVESTIGATORS IN SUBMISSION OF PROTOCOLS TO THE ETHICS COMMITTEE

Mistakes in submissions to Ethics Committee	
1	No submission to Ethics Committee
2	No consent form submitted
3	Consent form does not include possible adverse events
4	Available safety information not provided
5	Protocol does not include mechanism for reporting of adverse events and the management of intervention-related adverse events
6	Details of recruitment procedures such as advertisement are not included

team increases as the logistics need to be delegated to specific staff. Ideally, each site should have its own specific staff such as a pharmacist, study monitor and study nurse, and there should also be an overall project leader, data entry clerks, programmers and so forth.

Practical Problems

Number of Trials Investigators are Involved in

Often, investigators may be involved in several clinical trials at the same time. Serious problems may arise if the investigator is unable to attend all study meetings, does not devote time to solve problems that may arise during the trial, and does not supervise the clinic staff in an adequate manner. There is no magic number for the maximum number of trials an investigator should be involved in, as the amount of time devoted to clinical trials depends on his responsibilities within the trial (principal investigator or collaborator) and his commitments in the clinic or surgery.

Recruitment of Patients for the Study

One of the main practical problems of randomised clinical trials is the recruitment of patients in the study. This is usually a particular problem in single centre trials. Multi-centre trials may overcome this by having competitive recruitment where each centre's allotment depends on how fast recruitment occurs. Investigators need to be careful not to be over-optimistic of the recruitment rate, and methods to increase patient recruitment should be explored.

Groups Requiring Special Consideration

Clinical trials that focus on the effect of interventions on the elderly or very young children need special consideration. The dosage regime, adverse effects and documentation of outcomes in these special groups are unique and possibly different from young adults. In clinical trials of the elderly, it is important that the subject comprehends the contents of the consent form and willingly joins the clinical trial. Other special problems of the elderly include compliance with medication and transport to the clinic for further follow-up visits. In clinical trials that include children, care must be taken to ensure that written informed consent is obtained from the parents and that the study is also explained to the child. Verbal assent should be given by the child if the child is more than 6 years of age. In a randomised clinical trial of rigid contact lenses and the progression of myopia in Singapore children, special care was taken to explain the procedure of the trial and the nature of contact lens fitting to the adult as well as the child.

Informed Consent

Informed consent is a key part of the study and an item which the Ethics Committee or Institutional Review Board looks at very seriously. It is also a matter which auditors

examine closely. The important elements of the consent form can be found in the GCP guidelines and need not be reviewed here.²⁹ Important and controversial issues include language difficulties (the consent form should then be in the language of the patient), illiterate persons, mentally handicapped, children and unconscious patients. In general, informed consent should be taken from the patient but in extenuating circumstances, a next-of-kin or guardian may have to give consent. It is against GCP guidelines for the investigator to make the decision on behalf of the patient. As part of GCP, it is also important to complete all aspects of the consent form, which not only include patient's signature but date (to be written by the patient) and witnesses signatures.

Important Logistic Issues

Before the trial starts, a site initiation visit is usually required, particularly for multi-centre trials. This ensures that all the participants are familiar with the processes of the study, and allows queries to be raised over logistics or other matters. Important matters include what constitutes screening, inclusion and exclusion criteria, logistics of data and sera collection (special tubes, couriers), reporting of adverse events, patient compliance, indemnity and patient withdrawal, amongst others. It is vital that all investigators, particularly the principal investigator, understand the trial in-depth to ensure that no logistic issues hamper the successful conduct of the study. These issues are critical, particularly for investigator-initiated studies, where there is greater likelihood that logistic matters have not been fully worked out, leading to loss of samples and subsequently data. Other logistic issues that need to be addressed are the location of the trial—including where the patients will be seen, where the CRFs (case report forms) will be stored (lockable cabinet is mandatory), where the trial nurse will be located, how will she/he be contactable, how will payment for the trial be performed, under which account and how will this be used to pay for trial services (e.g. pathology services), storage and dispensing of medication, how to randomise patients, and so forth. The basic principle is that nothing should be taken for granted, and work-flow should be carefully and precisely thought through for each process for the trial from start to completion.

Important and Practical Issues in the Conduct of the Study

In sponsored trials, there is a monitoring team that ensures all data pertaining to the study are captured. Data sheets are analysed as they come in, so that missing or ambiguous data can be clarified. This is an infrastructure that is often lacking in investigator-initiated studies, but can be resolved by either having a data management group (e.g. Clinical Trial and Epidemiology Research Unit, APEC Centre for GCP, Department of Community, Occupational

and Family Medicine, NUS) or allocating responsibility for data management to a specific person. Standard operating procedures should be put in place to ensure that data are not lost along the way. Even more important are missing patients. It is the responsibility of the trial nurse to ensure patients are compliant with trial visits and trial protocol. Patients need to be reminded to take their trial medication with them when they travel—it is often forgotten. The principal investigator may need to provide a letter to customs and also a letter of introduction and contact should the patient become ill overseas. The clinical research nurse and the principal investigator need to work closely together so that the principal investigator is kept informed of any problems during the study. It is best to hold regular meetings to keep track of trial progress.

Clinical and laboratory data need to be recorded in CRFs as well as the patient's medical record file. The latter provides written documentation that acts as verification of the patient's progress. It is very important that both sets of records have similar entries, otherwise, this results in data discrepancy, a matter that auditors are particular about. The medical records also provide evidence that the patient exists and has attended the required visits. Additional data that need to be documented in the medical records are concurrent medication(s), any adverse event(s) (this means anything that happened to the patient whether related or unrelated to the study—by unsolicited questioning) and patient compliance. Serious adverse events, such as hospitalisation or death, need to be reported within 24 hours to the Ethics Committee and the sponsor company (in a sponsored study). In addition, the investigator has to be kept well-informed of adverse reactions that occur in trials conducted in other sites in a multi-centre trial and mechanisms to inform the patients and stop the trial should be in place. The nature of compensation should be explained to the subjects if serious adverse events occur as patient expectations may be different from that of the investigators. For example, if a patient is hospitalised for severe complications, will he or she be reimbursed for all medical treatment, hospital fees and surgeon fees? In a well-conducted study, where informed consent was adequately obtained, there seldom are voluntary withdrawals or dropouts (unless a patient, for example, goes for an extended overseas trip) as patients know exactly what to expect during the course of the study and do not have unexpected surprises. Letters to the patient's general practitioner are standard, but it is unclear whether these are useful in Singapore as many patients tend to attend different GP practices at different times.

For example, there was early termination of the aspirin component of the Physician's Health Study (a randomised clinical trial of the role of aspirin to prevent cardiovascular

disease and beta-carotene to prevent cancer) after 5 years of follow-up. The reason for the termination was a highly significant reduction ($P < 0.001$) in myocardial infarction risk in the aspirin group.³⁰ The patients were not treated with aspirin even after it was found to be an acceptable form of treatment for the disease. At what stage would the investigators stop the trial? What are the rules to follow when stopping trials? Often a stopping rule is established before the trial, whereby the limits for the test-control difference are set and if they are exceeded, the trial is stopped. However, stopping rules should be used only as a guideline and details further evaluated by the clinical trial committee.

The investigator should ensure that relevant forms such as CRFs may be accessible in an organised fashion after the study has ended. Even after the completion of the study, side-effects or benefits of the intervention may be present and the relevant forms may need to be retrieved. Informed consent forms, CRFs, laboratory investigation forms, medical records and correspondences should be kept for at least 2 years after the formal discontinuation of clinical development of investigational products or 6 years after the end of the clinical trial. As such, other factors that one may consider are the amount and availability of storage space and the possibility of off-site storage if there is insufficient storage space.

Finally, a word of warning: do not, under any circumstances, falsify data, even though the temptation to go back and fill in missing information or results may be very strong. These will inevitably be discovered and result in serious penalties. If certain items were forgotten or protocol violated during the study, it is best to record these as a file note and be open about the mistake rather than try to conceal it. Most experienced project leaders expect the occasional mistake and protocol violation (hopefully minor), but data falsification is an extremely serious offence that can jeopardise the entire study and credibility of the investigators. Fraud is a deliberate fabrication and alteration or omission of data deserves severe punishment, which must be distinguished from carelessness whereby a wrong observation, measurement or analysis was conducted. Fraud may be suspected if there is reluctance by the investigators to have a site-visit, if medical records are missing or not available or if correction fluid is used in the forms. If fraud has been detected, the nature of the problem has to be reported to the Ethics Committee and Scientific Committees immediately, whereby a thorough investigation may ensue. The results of the trial may be discarded if the problem is extensive and submitted manuscripts has to be withdrawn. In the worst-case scenario, the investigators may even be suspended from their jobs. An example of data fabrication occurred in the Bezwoda study in which there was disparity

TABLE IV: SUMMARY OF SPONSOR AND INVESTIGATOR-INITIATED TRIALS IN SINGAPORE (1997 TO 1999)

Types of trials	1997 No. (%)	1998 No. (%)	1999 No. (%)
Sponsor-initiated trials	36 (86.0)	70 (71.0)	86 (75.0)
Investigator-initiated trials	6 (14.0)	29 (29.0)	28 (25.0)
Total	42 (100.0)	99 (100.0)	114 (100.0)

Source: Ministry of Health, Singapore

between the case records and data, no signed informed consent was available, and there was no record of approval from the institutional review committee.³¹

Conclusions

An increasing number of sponsor-initiated and investigator-initiated phase III clinical drug trials have been conducted in Singapore. Table IV shows the comparison between the number of sponsored and investigator-initiated clinical trials in Singapore from 1997 to 1999. There is an increasing number of investigators interested and trained in initiating, conducting and completing such trials in Singapore. We have summarised the important issues and practical problems for both investigator-initiated and sponsor-initiated trials. For the investigator-initiated studies, there are numerous courses and the resources of the Clinical Trial and Epidemiology Research Centre and the Department of Community, Occupational and Family Medicine, National University of Singapore to assist with such studies. Advice from or collaboration with experienced investigators is another approach. At the Walter Reed Army Institute of Research in the United States, clinical investigators are required to attend one GCP course a year in order to maintain their investigator status. I wonder how many of our existing principal investigators fulfill this simple requirement?

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