"CLINICAL TRIALS"

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INTRODUCTION

There are many pitfalls in the path of investigations attempting to assess the efficacy of new drugs in the treatment of psychiatric disorders.

Among some possible sources of error are:—

1. The tendency of many psychiatric illnesses to improve spontaneously.
2. The role played by factors other than the pharmacological action of the drug in producing improvement, such as:-
   (a) the possible effects of suggestion and the therapeutic effects of the trial regime per se, particularly arising from the greater interest and time devoted to patients participating in the trial;
   (b) the effect of personally important factors in the environment of the individual which may influence the tendency to improvement or exacerbation during the trial period.
3. The possible influence of bias in selecting patients for a particular treatment and control procedure.
4. The influence of enthusiasm, bias and "halo" effects in rating clinical changes when the nature of the treatment undergoing trial is known.
5. The failure to obtain accurately matched treated and control groups in order to obtain clinically and prognostically similar groups for comparison.
6. The inadequate dosage of the drug not given for a sufficiently long period of time.
7. The effects of "carry over" when inert tablets are given after administration of active treatment.

Sir Austin Bradford-Hill, the father of clinical trials, stated in his classical book on medical statistics: "The clinical trial is a carefully and ethically designed experiment with the aim of answering some precisely framed question." He added, "in its most rigorous form it demands equivalent groups of patients concurrently treated in different ways."

Choice of Design for Clinical Trials

The following are some of the designs available for clinical trials:—

1. Matched-pair trial.
2. Cross-over trial.
3. Combination group trial for a combination of these methods.

Matched-pair Trials

The matched-pair trial is a controlled clinical trial carried out on pairs of patients, each pair consisting of patients identical in all relevant factors. One patient is given the treatment under evaluation and the other patient is given the alternative treatment or procedure. The relevant factors include constitutional attributes, form and severity of psychiatric disorder. Ideally, the pair should be comparable in clinical status and prognosis.

As it is probable that most psychiatric illnesses are heterogeneous disorders, even if we succeed in obtaining clinically identical pairs of patients of similar prognosis, there is no certainty that the pairs are sufficiently similar for scientific comparison, for they may differ in some important and relevant constitutional, biochemical, psychological or other attributes.

The Cross-over Trial

Here the patient serves as his own control and is exposed to more than one treatment, and it is assumed, with certain qualifications, that any differences between responses to two treatments within one patient are due to actual differences between the treatments.

The method has certain disadvantages, for example, the condition being treated must not be cured by the first treatment, otherwise the second treatment will have no opportunity of showing its worth. Similarly, the patient should be as severely ill at the start of the second treatment as at the start of the first treatment. Also, the effects of the first drug should have completely disappeared before the second treatment is started.

There is some evidence to suggest that the first treatment tends to have a greater effect due to suggestion and expectation. On the other hand, the second course of treatment has an advantage for there would be a greater tendency to a spontaneous recovery.

In view of the possibility that any clinical

change occurring during the trial period might be due to a spontaneous improvement or to factors unrelated to the pharmacological action of the drug, it is essential that the treatment and control procedures be given in different sequences in order to ensure that any factor which might influence the patient's clinical state would have the same chance of being coincident with both treatments.

If there are two treatments, for example, there are two possible treatment orders AB and BA. If there are three treatments, there are six treatment orders, ABC, ACB, BAC, BCA, CAB, CBA. Treatment orders should be allocated at random using device such as random number tables.

The great advantage of a cross-over trial is that it controls relevant factors within the patient and also environmental or non-pharmacological effects operating during the trial procedure.

Group-comparative Trials

In this design, different treatments are given simultaneously to similarly constituted groups of patients. The disadvantage of this method is the difficulty of recognising all possible relevant factors which might accidentally bias one or other group with regard to factors which could influence the outcome during the trial period, and this is one of the commonest reasons for failure in this type of trial.

It has the advantage of being the most practical type of trial and is not restricted either by the order in which the patients arrive for treatment or by the prevalence of the disease.

Apart from clinical characteristics, it should be similar in both groups in other important factors, such as severity and duration. It might be necessary to take age and sex into account if they are clearly relevant. Thus, if age and sex are relevant factors, there would be four 'random number' dispensing lists one for each of the four sub-groups defined by male-old, male-young, female-old and female-young. This is known as a stratified randomisation with stratification for age and sex to produce balanced groups.

Mixed Design

The disadvantages of matched pairs and comparative groups can be minimised by combining each with a cross-over design.

Criteria for Inclusion in the Trial

Precise criteria must be set out to which patients must conform before acceptance into the trial. These criteria may include clinical features and restrictions as to age and sex distribution, and also the presence or absence of previous treatment, and the duration of illness.

Criteria for Exclusion in Trials on Psychiatric Disorders

These psychiatric disorders include Schizophrenia and the affective disorders. Exclusions would include those with organic disease, including organic brain disease, and criteria relating to age, duration of illness, etc.

Methods of Assessing Change during the Clinical Trial

The following questions may be asked:-

1. By whom is the assessment to be carried out.
2. Is it to involve patient assessments or assessments by nurses or by the physician
3. If so, is it going to be one physician or two physicians making assessments independently?

A large variety of methods of rating clinical state are now available, for example, the Hamilton rating scale, the Beck rating scale, the Taylor manifest anxiety scale, and the Present State Examination (Wing).

When assessments are to be made, one has to decide how long and how many times before the beginning of the trial, how frequently during and after the completion of the trial, they should be made.

The form of measurements may be interval, nominal, or ordinal.

In the evaluation of the results, parametric statistics, such as the "*t*" test are suitable for interval measurements, and Chi-squared for nominal measurements. A variety of tests are available for ordinal measurements including the Rank sign test, the Mann Witney 'U' test, the Wilcoxson matched pairs, test, etc.

The numbers of patients required for clinical trials will depend on the degree of efficacy of the treatment under trial compared with the control procedure. However, graphs have been published by Clarke and Downey (1966) which help to estimate the number of patients required providing one can assess roughly how the trial group might respond. Similar tables are supplied by Maxwell (1968). The use of the sequential design may minimise the duration of the trial.

Side-Effects

It is important to note the side-effects occurring during the trial. It is particularly important to note the complaints which were present before the trial

started in order to avoid incorrectly attributing them to side effects of the drugs.

Side-effects which are spontaneously reported are likely to be more valid than those which are reported in response to direct questioning. If direct questioning is used, it should be standardised, for example, "Have the tablets disagreed with you in any way?

Drop-outs

It is important that full records be kept of all drop-outs together with reasons, for the effective evaluation of the drug and details included in the published report.

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Psychotropic drugs have changed radically the management of mental illness. However, a number of problems that have yet to be resolved have given rise to the situation where the difficulty of defining the pathophysiology underlying the various labels of mental disease coupled to the host of largely symptommatic medications, has resulted largely in empirical use of drugs. This should not be taken that empirical drug use has no place in modern medication – rather it must be viewed in the light that such a situation needs even greater care in evaluation of the drug therapy. The drug trial as a pointer to the efficacy or otherwise of a particular medication for a specified condition is, therefore, an important prelude to the widescale introduction of the drug.

Case for a Local or Regional Drug Trial

Practically all the psychotropic drugs used today originate from the laboratories of countries outside Asia and have been introduced into the market based on laboratory and clinical evidence obtained in a different context. The question in deciding whether there is a case or not for a drug trial in the local or regional context is not so much as to whether the drug is useful in the defined mental illness but rather how effective it is. To delineate the drugs of use to the region would require first hand knowledge and experience with their use; hence uncritical acceptance of the findings of others from a different time and a different setting need not necessarily hold. There are a number of considerations that would make the drug trial desirable especially for new medications.

The ethnic differences may be reflected in a difference in the pharmacodynamics of the drugs used due to metabolic or other differences. Cultural differences may lead to logistic difficulties of drug acceptance and continuance of treatment and the complication of taking native remedies at the same time as the psychotropic medication. For similar reasons pointed out, untoward effects may be manifest that had not previously been noted and these may be of such magnitude that would make the medication unacceptable medically or by the patient.

Competitive marketting on the part of the drug manufacturers has led to the production of a

large number of drugs and increased sophistication in marketting techniques make it difficult for the average user to distinguish between a pharmacological advantage or a gimmick with little therapeutic value. Only a properly carried out trial will prove the claim of therapeutic supremacy under the conditions as are existing in the area. Cost considerations are also important in countries which are relatively poor so that it would not be possible for such communities to indulge in the frivolities of drug prescription on the basis that the drugs may be of some value. A more positive approach based again on proven usefulness of the drug is the needed guide.

Some Problems of the Drug Trial

A brief survey of the various drug trials carried out in the region indicates that while a certain interest is seen, there are indications that there could be further improvement in the approach used. Some of the deficiencies include poor design, uncontrolled studies, inadequate assessment of the effects of drug therapy, conclusions based on impressions and without proper statistical analysis and uncertainty as to the purpose of the trial.

There may be a number of reasons for the above deficiencies.

There may be the attitude that since the drugs have met with success in other conditions, it was of little importance to validate it again and even if persuaded into doing so, a trial is done more as an exercise.

There could also be a genuine interest in the drug trial but the absence of trained personnel in planning, execution and evaluation of the project may result in a poorly-conducted trial. Where there are inadequate number of professionals and a relatively large number of patients, pressure of other more pressing medical care requirements make attention to drug trials of low priority.

The Development of Drug Trials in Psychotropic Medication

Drug evaluation in psychotropic medication is not an easy subject because of the peculiar circumstances that are attendant on the problem. However there are challenges not insurmountable with effort and even more important than taking them on as an academic exercise, this must be an accepted approach to psychotropic medication where there has yet to be found an adequate laboratory model reliable enough to predict the pharmacological properties of these drugs in man. Only in man himself can there be adequate study of the value of psychotropic drugs.

A more critical assessment of reports on psychotropic medication would serve as a useful starting point. A careful selection of the most promising ones for the purpose and a properly handled drug trial will give the best approach through the rapidly expanding and increasingly complex subject.

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INTRODUCTION

The evaluation of drug efficacy might be determined only after clinical trials. In the case of psychotropic medications, since there are no concrete and direct correlation between the animal studies and human trials, the role of the clinical trials, might be the most important for drug evaluation.

The establishment of trial conditions is also considered to be special because the drug should be tried in mentally suffering patients whose physiological, biochemical and morphological pathology is not yet unknown. Particular ethical problems exist for executing the trials in mentally handicapped persons whose legal responsibility is sometimes different from normal subjects.

To justify the clinical trials under these peculiar conditions, the purpose of the study, should be first defined clearly. According to the well defined purpose of the study, an adequate and well designed planning should be established. Furthermore, as there exist no objective physical or chemical parameters for the evaluation, double blind controlled trials are frequently required in all study phases. The needs for the implementation of studies in this case should be carefully analyzed.

The different purpose of clinical studies will be mentioned in this report, and then important checking items for the planning of the studies will be enumerated. In consideration of the above-mentioned matters, the ideal testing principle of the implementation of double blind controlled trials will be explained.

1. *Purpose of the Study*

Prediction and warning from pharmacologists and toxicologists on efficacy and safety – Documentation and evaluation

Before starting the clinical trials, the examination of preclinical data by clinical staff together with pharmacologists and toxicologists is of utmost importance. The assessment of the predictive value of the animal studies should be carefully evaluated. It should be reminded that this procedure is necessary not only for the future planning of clinical trials but also for the important ethical procedure of the trials in men. The initial determination of dosage schedule with the consideration of the possible adverse reactions should be made during the documentations.

2. *Determination of phamacokinetic and metabolic pattern in men*

The pattern of absorption, metabolism and elimination of administered drugs in men is often different from that in animals. The need for this study at the very early phase of clinical trials is stressed because the data should be referred back to animal studies to choose the animal species, the metabolic patterns of which are similar to human. The large-scale extended studies on safety and efficacy are to be performed by using these species of animal along with human clinical studies.

The phamacokinetic and metabolic pattern of drugs may in certain cases be different among the human races with different ethnological origins.

This is the so-called Phase II study and its implementation will be combined usually with tolerance studies.

3. *Tolerance studies – Initial sounding on the drug action (beneficial and non-beneficial) in healthy volunteers (including initial setting of dosage and administration.*

It is recommended that the trials will be performed in healthy volunteers and the dosage should be increased until a certain effect (beneficial or non-beneficial) can be obtained. However, since unexpected events have happened several times, this principle cannot always be applied.

In the Phase I study, the use of healthy volunteers has been recommended. However, it is sometimes obliged to use the patient from the first stage of the trials, especially in the case of major tranquillizers with the small dosage of which extrapyramidal symptoms are expected to appear.

The reaction type and sensitivity to the psychotropic medication between healthy persons and patients are often different.

It is seriously discussed now whether the normal subject should be used for the trials or not. The double blind trials in this phase are frequently needed for the subjective evaluations of reactions especially in the case of normal healthy volunteers.

4. *Determination of pharmacological spectrum and possible adverse reactions in patients (including determination of optimal dosage in patients).*

This is the so-called Phase II study. The purpose is to evaluate and confirm the preclinical predictions. The data obtained in this phase of the study will not be enough to support the usefulness of drugs in terms of efficacy and safety. The purposes of Phase II and III studies should be clearly defined because many of clinical practitioners have misunderstood them. The information obtained in this study will sometimes lead us to "feed back" to animal studies for reconfirmation. The information of Phase II study will be used as the basic sources for the planning of the Phase III trials.

5. *General assessment of efficacy and safety in patients.*

– *Large-scale controlled trials*
– *Long-range administration trials (Long-range safety study).*
– *Nature and frequency of adverse reaction*

To assess the efficacy and safety of new psychotropic drugs, the adequately planned and well designed controlled trials comparing with conventional drugs are required on the double blind

basis to avoid the different kinds of bias in doctors and patients. In the Chapter III, the basic principles and activities to be considered for the implementation of studies will be mentioned.

Most of the psychotropic drugs will be taken by patients relatively for a long period of time. Therefore the long-range administration study, if possible, for more than 6 months with the regular check of subjective adverse reactions, physical examinations and laboratory examinations are necessary. The residual and after-effects of drugs such as tardive dyskinesia, drug dependency liability (psychological and/or physical) and other general physical and psychological conditions during and after the medication should be verified by this study.

In this phase, the evaluation of the nature and frequency of adverse reactions comparing with the standard drugs and/or placebo will be performed. When the adverse reactions which are qualitatively special or unusual in addition to high in frequency are observed, the "feed back" to the animal studies will be necessary for verification.

The interpretation of the adverse reactions which are probably originated from exaggerated therapeutic actions is very delicate and difficult for analysis: The examples of this type of reactions are extrapyramidal syndrome of neuroleptics, somnolence and muscle relaxant activities of minor tranquillizers and anxiety attack and manic conversion of antidepressants.

6. *Monitoring on adverse reactions – Intensive and passive monitoring*

7. *Review on efficacy of drugs*

Not only in the case of psychotropic drugs but also in all drugs, the continuous review on safety and efficacy should be carried out reasonably even after the commercialization and during the whole life of drugs. The WHO is now organizing the International Monitoring System and the Japanese Government obliges pharmaceutical companies annually to report the adverse reactions for 3 years after the New Drug approval.

The review of the efficacy of the existing commercial drugs is being conducted mainly in the U.S. and Japan.

The technique for the intensive and passive monitoring and the role of the monitoring centre (on the hospital basis or the national basis) are studied now by the WHO group as well as health authorities and industrial groups respectively.

The attitude to evaluate the adverse reactions detected by every monitoring system and technique is still very much diversified. However, the international efforts on this matter are now started for the quick retrieval and evaluation of information.

II. *Planning*

When the purpose of the study is determined, the adequate planning should be made for each drug considering the available preclinical and clinical data on hand.

The following are the important items to be considered for planning.

1. Subjects: Healthy volunteers or patients, sex, age, ethnological aspects, patients' history, severity of disease, acute or chronic state, etc.
2. Number of subjects:
3. Establishment of dosage and administration schedule
4. Ethical considerations – consent of trial subjects.
5. Observation parameters (objective and subjective)
   - Physical and biochemical parameters.
   - Rating scale
6. Comparative or non-comparative trials
7. Controlled trials, especially simultaneous comparison under randomly allocated condition
8. Open or blind (single and double) study

In principle, children, childbearing women and aged persons should not be included in the trials before the Phase II study.

The number of patients in each trial will be determined empirically and also roughly estimated statistically in the case of the controlled trials. However, the number of patients estimated by statistical calculation will generally be more than actually available number for the trial due to the fact that it is statistically or empirically impossible to decide the reasonable number of patients. Therefore, certain compromise might be made between the statistical and practical aspects.

The procedure of obtaining the consent from trial subjects is extremely difficult. This will vary from country to country, and according to the type (or phase) of studies, consent will be required case by case, orally or with a written form.

The observation parameter for the efficacy and subjective adverse reactions is mainly made based

on the psychological questionaire, i.e. the rating scale.

Generally, the doctor's questionnaire (Dr's rating scale) and the patient self rating scale will be applied simultaneously for the evaluation of minor tranquillizers. The nurse's rating scale may be useful for the evaluation of antipsychotic drugs in case of the hospitalized patients.

Certain practitioners still prefer the comparison of new drug experiences with the former treatment history or experiences. However as a trustful way, the simultaneous comparison should be justified with regard to the scientific attitude of trial. At the same time, the allocation of drugs to patients should be made at random as well as trial drugs and standard drugs. In this case, the double blind study will be needed to avoid the bias of doctors and patients.

In psychotropic drug studies, the treatment period for double blind studies should be limited because long lasting double blind studies disturb practically and ethically the management of patients. Generally, the effects of drugs will appear within a few weeks if the drug is effective.

For the safety studies, a rather long administration period will be required and in this case, the open studies are generally applied. The adverse reactions observed during the double blind study should be compared with those in the open study, and the rational medical interpretation of the reactions must be made finally. The predictive value concerning the adverse reaction data obtained during the double blind trials might be different from that of the open study.

III. *Implementation of Double Blind Controlled Studies*

As already mentioned, the need of double blind controlled trials is justified for most of the psychotropic drug studies, especially for the evaluation of usefulness.

The following are the activities of the trial team consisting of medical doctors, biostatisticians and medical monitors of pharmaceutical companies (when the trial is requested by industries) which are necessary for the planning, execution, data processing, evaluation of data and follow-up after the completion of double blind studies.

1 – Planning

1 – 1 Hypothesis

1 – 1 – 1 Medical hypothesis

Drug A may be more effective than Drug B. This hypothesis will be valid in _____symptoms which will appear in_____ disease but may not be true in_____ symptoms of the disease.

1 – 1 – 2 Statistical hypothesis and evaluation principle

1 – 1 – 2 – 1 Null hypothesis H_0 A = B

Alternative hypothesis

H_1 A > B (one tailed)

or

H_1 A ≠ B (two tailed)

1 – 1 – 2 – 2 Hypothesis on distribution of observed or statistical value

1 – 1 – 2 – 3 Determination of rejection region and critical value – Determination on probability

1 – 1 – 2 – 4 Determination of the rule of test

Reject H_0:

Observed value (or statistical value) $\geq$ Critical value

1 – 1 – 2 – 5 Observation (i.e. implementation of experiment)

1 – 1 – 2 – 6 Test for verification of hypothesis (statistical work)

– If the observed data correspond to the rule 1 – 1 – 2 – 4, the result is not accidental under H_0 but inevitable under H_1, ie.. rejects H_0 in the degree of risk α. This is also expressed as follows; the difference between A and B is significant with the significance level α. α means the probability of misjudging A to be B when A ≠ B is a fact.

Probability α : type of 1 error (error of overstating)

* If the data do not fit the rule 1 – 1 – 2 – 4, the result accepts H_0. A and B are not significantly different. When H_0 is accepted by misjudgement despite the fact that H_1 should be accepted, error of overlooking is made. The probability of error of overlooking is β.

Probability β : type of II error (error of overlooking)

1 – 1 – 2 – 7 Interpretation of the statistically stated conclusion

– Significant difference

Medical interpretation of observed difference

*– Non-significant difference
To check the value of β against the difference δ which might be the medical problem. In this case, the evaluation of detection power, i.e. probability $(1-\beta)$ should be necessary.

* In the case of drug evaluation study, generally β cannot be considered because the one tailed test will be used usually for data evaluation. (For example, Chi-square test)

1 – 2 Study design

1 – 2 – 1 Group comparative trials

1 – 2 – 1 – 1 Simple randomization

B C A C B B A (randomized)

1 – 2 – 1 – 2 Stratified randomization

Stratum 1 B C A C B B (randomized)

Stratum 2 A C C B A C (randomized)

1 – 2 – 2 Matched pair trials

1 – 2 – 2 – 1 Matched pair

A B A
B A B

(randomized)

1 – 2 – 2 – 2 Randomized blocks

B A C
C B A
A C B

(randomized)

1 – 2 – 2 – 3 Cross over trials

	1st Treatment	2nd Treatment
Patient 1	A	B
" 2	B	A

	1st Treatment	2nd Treatment	3rd Treatment
Patient 1	A	B	C
" 2	B	C	A
" 3	C	A	B

Reference: Maxwell, C.: Clinical Trial's Protocol, Stuart Philips (1969).

1 – 3 Drugs
1. Test drug
2. Standard or reference drug(s)
3. Placebo (inactive)
4. Quality control of trial drug(s)
5. Rule and restriction on accompanied general treatment.

1 – 4 Dosage and administration
1. Dosage fixed – flexible
   flexible – fixed
   fixed
2. Duration of trial and aftercare of trials.
3. Necessity of wash-out

1 – 5 Trial institution
1. Hospital (Psychiatric and/or general)
2. Clinics (out patients)
3. Multi-clinical study

1 – 6 Trialists
1. Experience in the specialized field
2. Group study
3. Role of paramedical personnel (nurse, psychologist, etc.)

1 – 7 Patients selection
1. Stratification and exclusion (children, aged patients, childbearing women, etc.)

1 – 8 Randomization and allocation
1. Collaboration of biostatisticians
2. Role of 3rd party controller for keeping trials fair

1 – 9 Rating of effectiveness
1. General improvement rate (G.I.R.)
2. General severity rate (G.S.R.)
3. Symptoms rating scale
4. Patient self rating scale

Quantification of scale

1 – 10 Adverse reaction
1. Comparison with placebo and/or standard drug
2. Laboratory data

1 – 11 Drop-out and discard case (Setting the rule for follow-up and handling).

1 – 12 Handling of unexpected adverse reaction during trials

2 Execution of trials

2 – 1 Confirmation and follow-up or recording process

2 – 2 Confirmation and stock of drugs and distribution to patients (Role of pharmacists)

2 – 3 Confirmation of random allocation of patients for trials

2 – 4 Confirmation of drugs intake by patients.

2 – 5 Follow-up of dosage schedule for each patient.

2 – 6 handling and treatment of adverse reaction

2 – 7 Follow-up of drop-out cases and handling of discard cases (replacement).

3 Evaluation of data
3 – 1 Documentation before key-open
Confirmation of fairness of trials
Blindness
Random allocation
Constancy of rating
3 – 2 Data processing
3 – 3 Medical interpretation of statistical data
1. Significant level
2. Meaning of applied statistical technique
3 – 4 Pooling of data
4 Follow-up of patients after trials
1. Relapse
2. Residual effects
3. Long-term effects
4. Recovery of non-used drugs

The planning is the most important step for trials. The collaboration with biostatisticians and pharmacists will be required for this purpose. Although doctors do not have to be biostatisticians by all means, they should be able to understand the meaning of statistics, especially how to translate medical hypothesis into statistical hypothesis, and accordingly should design the trial.

In the checking items, 1 – 1, and 1 – 2, the short explanation on the statistical hypothesis and the type of experimental design are shown. Even though the statistical difference between the new drug and the standard drug (or placebo) is demonstrated, the final medical interpretation on the difference should be explained.

In the case of clinical trials, the handling of β is almost impossible.

Generally, the placebo is used in Phase I study and the active control drugs (i.e. standard or difference drugs) in Phase II and III studies.

The standard drugs should be selected from already commercialized and widely used drugs according to the target indication and the method of trials.

The quality control (appearance, color, odor, taste and dosage of active drugs, content of active ingredients and disintegration time of pharmaceutical form in artificial stomach or gastric juice) should be verified by the third party if possible.

The drugs to be used occasionally for the general accompanied treatment such as hypnotics, gastrointestinal remedy, analgesic-antipyretic, etc. should be standardized to avoid the interaction with the trial drugs.

The dosage schedule will be designed according to the previous experiments, target indications, the nature of drugs and the study setting.

The fixed/flexible schedule is used mainly for the minor tranquillizer evaluation.

The wash-out of formerly administered drugs will be sometimes required before the trial and in the case of cross-over design. However, the wash-out is not absolutely necessary if the treatment period is sufficiently designed.

The multiclinical studies are now frequently organized for the purpose of obtaining enough number of patients and gathering the actual and realistic information. In this case, the planning meeting plays an important role.

The trialist should understand and be accustomed to the controlled trials, and be trained for the rating with the neutral attitude. In this connection, preliminary validity test on the rating attitude of trialists may be required in the case of group or multiclinical studies.

The stratifications of patients seems to be quite difficult and the matched pair design based on the sequential analysis used for psychotropic trials has been discussed frequently as regards the validity of the methodology.

It is required to appoint the controller(s) who randomized the trial drugs and patients, keeping the key table and checking the fairness on the trial design, execution and data processing.

For an evaluation, the general improvement rate (G.I.R.) evaluated by doctors (and patients) may be the most useful information to assess the efficacy of drugs. This rate may be measured by the final judgement by trialists using the terms of improvement, non-improvement or aggravation.

General severity rate (G.S.R.) may be less valuable and despite of its difficulty for evaluation because the starting point of severity in each patient may be different due to the difficulty of stratification of patients.

Quantification of rating scale is an insoluble problem. There are different kinds of proposals. We are using the most suitable way which will fit in each trial design.

The adverse reactions should be carefully checked and rated. Usually, the comparison will be made on 30% of confidence level when compared with placebo, and on 5 – 10% level of confidence when compared with standard drugs. We observe sometimes the adverse reactions (also in laboratory data) in a placebo group.

The follow-up of drop-out cases is very important and these cases should not be omitted when the data is evaluated statistically.

How to judge the effects of drugs in drop-out cases is also an important problem. The most

severe attitude is to include the drop-out cases in the not improved ones when the follow-up of patients is impossible.

The discard case which is usually caused by inattention of trialists as regards the selection of patients should be avoided as much as possible.

When adequate and well designed planning is established, the trials are to be executed based on the rules established previously.

When we evaluate the obtained data, it should be kept in mind that the fair and reasonable medical interpretation is extremely important. Recently, a lot of trialists have suffered from a peculiar disease, the so-called "Significantitis" and often forgotten the medical interpretation.

The follow-up of the trials is also important. When the hypothesis is not proved, the judgement on the necessity to repeat the trials should be attentively considered.

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Controlled clinical trials are designed to ensure that comparisons of different treatments are as precise as informative and as convincing as possible. The basic techniques of such trials have been well developed and widely publicised in the last 30 years. Nevertheless, many trial reports, certainly in the sub-speciality of leprosy, and I suspect in other branches of medicine, reveal important faults in planning, methodology and analysis. The following generalisations are based on experience gained in eleven controlled trials and seven pilot trials carried out at the Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Malaysia, over the past 14 years.

The Protocol

For any trial to be successful, careful planning is required, including the production beforehand of a detailed protocol. This should clearly and concisely summarize the entire plan of the trial, including the aims and objects, drug regimens to be followed and their duration, the number of patients required, including their selection and allocation, the examinations and investigations to be performed before and during the trial, the methods and frequency of assessments, any special investigations required in view of the known or anticipated toxicity of trial drugs, the policy for interruptions in treatment and intercurrent disease, and wherever possible the tests to be carried out to ensure that trial drugs are in fact being taken and absorbed (Waters, Rees and Sutherland 1967).

Patient Selection

Careful selection of patients is essential. We have found it better to keep to a defined group of patients despite any resulting delay in intake, rather than broaden the basis for admission. For example, recent work from the Leprosy Research Unit and its collaborators has shown that there are four distinct and different mechanisms of peripheral nerve damage in leprosy (Pearson, 1972). Thalidomide is very effective treatment for one, but only one, of the four (Sheskin, Magora and Sagher, 1969; Sheskin and Sagher, 1971; Waters, 1971 b), namely the immune complex complication (Wemambu *et al.*, 1969) known as Erythema Nodosum Leprosum (ENL). In drug trials in leprous neuritis, to include all cases without regard to aetiology would be highly misleading. Precision in psychiatric diagnosis, related as it usually is to well-recognized symptom complexes rather than to proven aetiologies, may well be more difficult. However, careful analysis of individual as well as group assessments should be considered; the discovery of anomalous results in a proportion of patients might provide new insights into the classification and perhaps even the aetiology of mental disease.

Control Regimens

The choice of the control regimens depends on the condition under investigation. In some diseases, current standard therapy is required, e.g. dapsone (DDS) in untreated leprosy or penicillin in General Paralysis of the Insane (GPI). In others, placebo tablets may ethically be given. Wherever possible, both trial and control drugs (or placebo) should be used in identical preparations, thereby allowing the "double blind technique" to be employed. This is always desirable, but is particularly important in psychiatric studies where so many of the assessments have perforce to be relatively subjective. Reputable drug firms are most co-operative in the supply of identical placebo and trial drug capsules or tablets, and will also manufacture unusual (and to the patient, unrecognizable) preparations of standard drugs, if these appear psychologically desirable to avoid bias on the patient's part (Pearson and Helmy, 1973).

Methods of Allocating Patients to Treatment Groups.

What is invariably essential is the random allocation of patients to the two (or more) treatment groups being compared, in the knowledge that this method will yield series of patients whose condition is similar at the start of treatment; any differences between the series, whether in known or unknown factors of prognostic importance, will be small and within chance limits. We have found that the most satisfactory practical method of allocating patients to groups is to have a sequence of numbered opaque sealed envelopes prepared in advance by a statistician each containing a slip bearing the serial number, and a predetermined treatment allocation corresponding to it. When a suitable patient is admitted to the trial, the patient is assigned to the next free serial number, the appropriate envelope is opened, and the patient is placed in the treatment series indicated. When the response to treatment is known or believed to be affected by a characteristic of the patient (such as race, age or sex) or of the disease (such as a measure of its severity), the device of "stratification" should be employed at the allocation stage. It is usual to arrange the random allocations so that totals of patients in each treatment series remain closely similar as the intake proceeds for otherwise quite large differences might arise by chance, for example as a result of seasonal weather effects: psychiatric breakdown may be precipitated by a pre-monsoon heat wave, and ENL neurities by the stress of a rainy or cold season.

After allocation, the management, observation and assessment of all patients must be closely similar, so that any differences in response can be ascribed with confidence to the difference in treatment.

"Cross-Over" Trials

Where a disease condition persists for many months with little alteration in its severity, an alternative trial design is to use the patient as his own control (Sheskin, 1965; Sheskin and Sagher, 1971; Waters *et al.*, 1967). This method is not applicable where the treatment is believed to effect radical cure, e.g. antibiotics in bacterial meningitis, penicillin for GPI or Vitamin B12 for subacute combined deneration of the cord, but it is particularly attractive in the study of psychotropic drugs. We have ourselves used it widely in ENL trials, and the methodology utilized in a study of the effect of thalidomide in severe ENL is shown in Figure 1 (Waters, 1971a). The trial consisted of four 4-week periods, and during each the severity of the ENL was assessed by the total weekly prednisolone requirement (in mg) just sufficient to suppress the principal symptoms and fever of the reaction. An initial (control) period was followed by a second, in which, depending on random allocation, either thalidomide or identical placebo tablets were prescribed, the reverse treatment being given in the third period. A fourth (or final control) period was included to confirm that the ENL remained at, or returned to, approximately the same degree of severity as in period 1, i.e. spontaneous worsening or remission was excluded. Although the trial was double

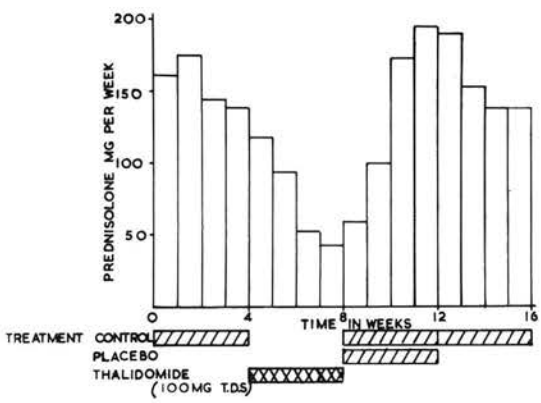

Figure 1: Double-blind trial design, 16-week schedule, for the effect of thalidomide (300 mg daily for 4 weeks) on prednisolone dosage in severe chronic erythema nodosum leprosum; representative result from an individual patient (Waters 1971a).

blind-indeed no one in Malaysia knew the tablet code until it was completed – two difficulties were encountered. First, the dates of the different trial periods were known to the doctor prescribing the prednisolone and theoretically bias in prescribing could have occurred at period change-over dates. In two more recent trials (Pearson and Helmy, 1973; Waters and Helmy, 1973) we have succeeded in making the dates of the individual trial periods effectively double-blind by utilizing treatment periods of two different durations, randomly allocated and known only to the drug dispenser. The second difficulty was that some patients complained of sleepiness during either period 2 or 3. The problem of both patient and doctor bias developing because of recognizable trial-drug side effects is less easily overcome, and is a major difficulty in studies of many psychotropic drugs.

Assessments.

Unless double-blind techniques are being employed, all assessments should be performed by Independent Assessors. This is usually simple to arrange for most objective assessments, e.g. nerve conduction velocities and voluntary muscle tests in neuritis, or serial EEG reports in epilepsy, but is frequently difficult in psychiatric assessment where patients may exhibit resentment and/or aggression against an 'outside' (independent clinical) assessor. In the more subjective clinical assessments, for both psychiatric and organic conditions, definitions of the different grades of severity used in scoring a sign or symptom should invariably be given. To state baldly, for example, that, "Anxiety was assessed according to four arbitrary" (and undefined) "grades of severity", makes a trial both unreproducible by, and the results less acceptable to, other workers.

Finally, controlled clinical trials are time consuming and exacting procedures. Before embarking on one, it is welll to ensure that the aims and objects specified are likely to be achieved by the trial design utilized, taking into account knowledge already gained of the properties of the trial drug from one or more pilot trials performed in a similar, if smaller, and equally carefully – selected group of patients. I have known one carefully conceived and executed controlled trial produce a negative result, solely because the dosage of the trial drug was too small to produce significantly the therapeutic effect under investigation (Pettit, 1967).

SUMMARY

From experience gained in the Leprosy Research Unit, Sungei Buloh over the past 14 years and from 11 controlled and 7 pilot trials, certain aspects of controlled drug trial design are discussed. It is recommended that a full written protocol should be produced before the start of any trial. The need for careful patient selection and of random allocation of patients to the different treatment series is emphasized. Certain practical difficulties encountered in double-blind trials using the patient as his own control ("cross-over trials") are discussed.

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