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PHASES OF A CLINICAL TRIAL

Phase I of clinical trial is done on human volunteers to study the pharmacokinetic properties (time-concentration) of the regimen, to investigate toxicity, major side-effects, and to delineate the maximum tolerated dose. The last may require dose escalation. It may not be easy to find volunteers for this kind of trial, except possibly hopeless cases who find a ray of hope in the new regimen, or courageous, many times healthy people, who agree to participate for some inducement. The inducement should be proportional to the expected discomfort and not excessive that could be frowned upon as coercive. Note that healthy subjects can also be used in this phase because therapeutic efficacy is not an issue at this stage. This phase generally needs 30 to 60 participants.

Phase II of a trial is done on patients for which the test regimen may be eventually indicated. The objectives of this phase are to investigate potential efficacy in a clinical setup, short-term incidence of side-effects, identify a dose schedule for various kinds of cases (such as for mild, moderate, severe; or for children and adults), and to collect further pharmacologic data. Phase II trial could also compare drug induced effects in individuals with and without comorbidities or on other drugs (in this phase there is no need to exclude such patients) that will help define exclusion criteria for phase III trial. Beware that comorbidities can skew and confound the drug effect. Do not restrict too much because generalisability would suffer.

Phase II also establishes or refutes that the new regimen is likely to meet at least the minimum level of efficacy. If this level is not met, there is no use of pursuing the regimen any further. This is a crucial phase that really establishes that the regimen is going to be useful or not. The number of participants in this phase is generally 100 to 300. Sometimes it is a randomised trial with a control group on the pattern of a phase III trial. Failure of phase II can help in identifying the problems with the regimen and to go back to the basics to improve it.

Phase III is a large-scale trial to establish the efficacy and safety. There must be a control group in this phase, and the subjects are randomly allocated to the **test arm** and **control arm**. For this reason, this is called a **randomised controlled trial** (RCT). At least 300 subjects are generally recruited for each arm of this trial. The exact number depends on the statistical considerations. The number can go upto several thousands. The follow-up must be sufficiently long for efficacy and side-effects to emerge, and to rule out that any relief to the patients is transient. It may take upto 10 years from start of phase I to finish of phase III. Successful completion of phase III allows you to apply to the regulating agencies to market the drug.

A very important research these days emanates from monitoring of side-effects of a drug after it is marketed. Patient preferences due to cost, ease in injestion, ready availability, etc., are also evaluated. This is called **postmarketing surveillance** and many times considered as phase IV of clinical trial. All adverse reactions or any such event attributable to regimen are monitored. The effectiveness in actual conditions is also evaluated. Recent findings about

tamoxifen carrying a risk of endometrial cancer, and arthroscopic surgery not beneficial for osteoarthritis of knee are the results partially attributable to such surveillance.

Adapted from:

Basic Methods of Medical Research, Fourth Edition, 2018 by A. Indrayan

Details at

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http://www.medicalbiostatistics.com/Medical_Docs/MedicalResearchBook.pdf