A REVIEW ON CLINICAL TRIALS: WHY TO INTRODUCE ZERO PHASE

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ABSTRACT

Objective: The main objective of this study is to know clinical trials in nutshell and phase 0 clinical trial are to establish at the very earliest opportunity before large numbers of patients have been accrued and exposed to potential drug-associated toxicity whether an agent is modulating its target in a tumor, and consequently whether further clinical development is warranted. We review here the fundamental requirements of clinical studies conducted under an exploratory IND and address some common misconceptions regarding phase 0 trials. Phase 0 clinical trials, developed in response to the United States Food and Drug Administration (FDA)’s recent exploratory Investigational New Drug (IND) guidance, and are intended to expedite the clinical evaluation of new molecular entities. The exploratory IND supports the performance of first-in-human testing of new investigational agents at subtherapeutic doses based on reduced manufacturing and toxicologic requirements, allowing the demonstration of drug-target effects and assessment of pharmacokinetic-pharmacodynamic relationships in humans earlier in clinical development.

Conclusion: From this present review study, we concluded that Phase "0" in clinical trials can work as a useful parameter to measure drug safety at subtherapeutic level and the fundamental requirements of clinical studies conducted under an exploratory IND and address some common misconceptions regarding phase 0 trials.

Keywords: clinical trials, clinical trial phases, zero phase.

INTRODUCTION

A clinical trial may find that a new strategy, treatment, or device[4]

- Improves patient outcomes
- Offers no benefit
- Causes unexpected harm

PURPOSE OF CLINICAL TRIAL

At the beginning of the AIDS epidemic, people with HIV and AIDS flocked to clinical trials. At that time, no anti-HIV medications were available by prescription. The only way to get HIV treatment was through clinical trials. The medications were experimental - researchers did not know exactly what effects they would have in humans. But people were willing to take the risk; there were simply no other options. Even though there are approved medications for HIV, clinical trials are still extremely important. Researchers are working to develop medications with fewer side effects and easier dosing. These treatments must be tested in clinical trials. There are also trials that test different combinations of approved medications, and trials without medications (called observational trials) that look at behaviors or study disease progression. [6, 7]

The purpose of clinical trials is to discover

- if a drug works and how well
- if it has any harmful effects
- its benefit-harm-risk profile - does it do more good than harm, and how much more

Before a medication or treatment is used in the general public, it must be tested. There are 3 phases of clinical trials that a treatment needs to be evaluated in before it meets the criteria for FDA approval.

- Phase 1 trials – These trials are conducted on a small number of people and are designed to see if a treatment is safe.
- Phase 2 trials – After a treatment is considered to be relatively safe, it is evaluated in a phase 2 trial to see if it is effective.
- Phase 3 trials – If a treatment is found to be relatively safe and effective, it is then evaluated in a phase 3 trial to see if it is more effective than standard treatments available, or has fewer side effects than standard treatments. [8]
Comparison of clinical trial phases

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<td>Several months</td>
<td>Several years</td>
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Who sponsor clinical trials?

The National Heart, Lung, and Blood Institute (NHLBI) and other National Institutes of Health (NIH) Institutes and Centers sponsor clinical trials.

Many other groups, companies, and organizations also sponsor clinical trials. Examples include Government Agencies, such as the U.S. Departments of Defense and Veterans Affairs; private companies; universities; and nonprofit organizations. [10] In the US, sponsors may receive a 50% tax credit for certain clinical trials. [11]

Types:

One way of classifying clinical trials is by the way the researchers behave.
1. In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.
2. In an interventional study, the investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment. Then the researchers measure how the subjects' health changes.

Another way of classifying trials is by their purpose. The U.S. National Institutes of Health (NIH) organizes trials into five different types:[12]
1. Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes. 2. Screening trials test the best way to detect certain diseases or health conditions.
3. Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
4. Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
5. Quality of life trials (supportive care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.
6. Compassionate use trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.[13] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

A third classification is whether the trial design allows changes based on data accumulated during the trial.
1. Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins and do not assess the results until the study is complete.
2. Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.[14] Adaptive trials often employ a Bayesian experimental design to assess...
the trial’s progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.[15] The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.[16, 17]

PHASES OF CLINICAL TRIALS

The phases of clinical research are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment. In the case of pharmaceutical study, the phases start with drug design and drug discovery, go on to animal testing, then start by testing in only a few human subjects and expand to test in many study participants if the trial seems safe and useful.

Pre-clinical studies

Preclinical studies evaluate the effects of potential therapeutic interventions in cells and animals, and are used to select candidates for entry into clinical trials based on effectiveness in disease models and safety. All drugs require data from various toxicological preclinical studies to support their potential safety in humans before clinical trials can begin. [18] This is known as preclinical research. It’s carried out in the laboratory in test tubes, known as in vitro research, and in living organisms, known as in vivo research. Computer technology is also used. [19]

Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the United States Food and Drug Administration’s (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. [20] Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent’s pharmacokinetics. [21]

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers will be recruited. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organizations (CROs) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer. [22] In addition to the previously mentioned unhealthy individuals, “patients who have typically already tried and failed to improve on the existing standard therapies” [20] may also participate in phase I trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre.

There are different kinds of phase I trial

Single ascending dose (Phase Ia)

In single ascending dose studies, small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time to confirm safety. [23] Typically, a small number of participants, usually three, are entered sequentially at a particular dose. [20] If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose. Multiple ascending dose (Phase Ib)

Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level. [23]

Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug while fasted, and after being fed.

Phase II

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. Phase II trials are performed on larger groups (100-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. [20] When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

- Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).
- Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design

Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized controlled trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Phase III

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. The percentage of Phase II trials that proceed to Phase III, as of 2008, is 18%. [24] Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. [20] This is
sometimes called the “pre-marketing phase” because it actually measures consumer response to the drug. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at “label expansion” (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as “Phase IIIb studies.”[24, 25]

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug’s safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), or the EMA (European Union).

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the “regulatory submission” that is provided for review to the appropriate regulatory authorities [26] in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines through a New Drug Application (NDA) containing all manufacturing, pre-clinical, and clinical data. In case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.[27]

Phase IV

Phase IV trial is also known as postmarketing surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

The entire process of a drug from lab to this point may take approximately 12 to 18 years, often costing over $1bn. [28, 29]

Phase V

Phase V is a growing term used in the literature of translational research to refer to comparative effectiveness research and community-based research; it is used to signify the integration of a new clinical. [30]

Role of pharmacist in clinical trials

According to recent honesty & ethics survey by gallop, there are three resources that patients consistently turn to for health-related information:

- Nurses
- Pharmacists
- Physicians

Pharmacists are not only highly trusted; they are also highly accessible. On average, American patients visit pharmacies at least five times more than they visit their doctors. This puts the pharmacist in an ideal position to provide patient education materials on a wide variety of health-related topics, including clinical research trials - a subject the general public knows little about. And it makes marketing to pharmacists an intelligent tactic for pharmaceutical companies.

While pharmaceutical companies have used newspaper, radio and TV ads to recruit patient participation in clinical research trials, the crowded spaces of traditional media channels may make future successes dependent upon their ability to maximize nontraditional approaches. Given the trust that patients have in pharmacists—and the frequency with which they see them—Pharmacists could play a vital role in educating and engaging the public about clinical research trials.

In 2010, the center for information and study on clinical research participation (CISCRRP) conducted a study on public receptiveness to receiving clinical research trial information from pharmacists. The results were overwhelmingly positive: 80 percent peoples respondents said they would like to receive clinical research trial information from their pharmacists.

A follow-up study in 2012 was conducted to test the knowledge and interest in clinical research trials after patients had received information from pharmacist. 32 pharmacists at different locations participated in displaying/distributing patient education materials about clinical research trials, and 487 patients were surveyed. Again the results were positive: patient confidence in and knowledge of clinical trials rose from 10 to 20 percent. [43]

Patient education isn’t the only way pharmacists could help market pharmaceutical products, however, they could also play a vital role in the vetting process, due to their personal knowledge of patient’s medical histories.

Introduction of Phase “0”

A Phase 0 trial is an important element of NExT (NExT stands for the NCI Experimental Therapeutics program). NExT is a collaboration between two divisions within the National Cancer Institute (NCI) – the Division of Cancer Treatment and Diagnosis (DCTD) and the Center for Cancer Research CCR). It promises to shorten -- by up to six to 12 months -- the timeline for taking anticancer drugs from the laboratory to the clinic. Specifically, a Phase 0 (Phase zero) clinical trial is designed to study the pharmacodynamic and pharmacokinetic properties of a drug. Pharmacodynamics (PD) describes the biochemical and physiological effects of a drug on the body, including how the drug is absorbed, moves throughout the body, binds to various structures, and interacts with certain molecules within target tissues. Pharmacokinetics (PK) describes the activity of a drug in the body over a long period of time. This includes the process by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted. Considered together, data from pharmacodynamic and pharmacokinetic studies help researchers determine a rational dosage regimen for testing in clinical trials.[31]

Unlike a Phase I trial, in a Phase 0 trial, a limited number of doses, and much lower doses of the drug are administered, therefore there is less risk to the participant. Also, fewer patients are needed (about 10-12 patients, on average in a Phase 0 study vs. about 20-25 patients in a Phase 1 trial). By studying PD and PK, researchers can weed out the drugs that aren’t producing the desired effects much more quickly, and they can avoid moving these drugs onto Phase I, II, and III trials.[32]

Advantages of conducting a Phase 0 trial

Due to their design, Phase 0 trials can be conducted in less time with fewer patients than Phase I trials. By conducting a Phase 0 trial on a particular drug, the process for Phase I and II trials on that drug is accelerated. Additionally, because Phase 0 trials study how the body reacts to the drug and how the drug acts in the body, if a drug is found to react poorly or to have serious side
effects, the testing for that drug can be stopped sooner, without the additional expense of further trials. As a limited number of low doses of drug are given in a Phase 0 trial, the risk to the participant is minimal, if any.

Additional benefits of Phase 0 trials include the following:

- Because the toxicology testing required prior to initiating Phase 0 clinical trials is reduced due to the low doses of drug used, these trials can be initiated substantially sooner than the standard Phase 1 study.
- Phase 0 trials could facilitate rational drug selection, identify therapeutic failures early, and compress timelines for anticancer drug development.
- Phase 0 trials provide initial rationale and guiding principles for further drug development based on studies in humans (rather than xenografts, where tissues of one species are transplanted to another species).
- Phase 0 trials that focus on extensively characterizing how a drug works and whether it hits its intended target (including molecular imaging studies) in a limited number of patients could yield results that would optimally inform and expedite the subsequent development of molecularly-targeted agents.
- The results of Phase 0 trials can improve the efficiency and chance of success of subsequent trials.
- Phase 0 trials could help to evaluate the effects of an agent at the molecular level, select the lead agent from a group of compounds, and assist in optimizing the selection of the starting dose for subsequent studies. In addition, these studies can aid in developing reasonable dose escalation schedules, whereby doses of a drug are slowly increased over time in order to find the highest dose with an acceptable level of adverse side effects in the patient.[33]

Why is NCI taking the lead on developing Phase 0 trials?

Despite increasing investment in new drugs, the rate of approval of such drugs by the U.S. Food and Drug Administration (FDA) to treat cancer remains low. Drugs continue to fail due to lack of efficacy or associated adverse events. Additionally, good screening tools that can accurately predict whether a new drug will be active or toxic are not available. Finally, timelines for development and testing of new drugs remain excessive. Seventy percent of oncology drugs that enter Phase II testing fail to enter Phase III, and for those that enter Phase III testing, 59 percent eventually fail. Moving from Phase I to Phase III often takes more than a decade.[34]

**Figure 2: Process of clinical trials.**

**Phase 0 (Zero) clinical trials: A myth or reality?** [35]

Phase 0 trials are the first human trials with no therapeutic or diagnostic intent, with a limited number of patients (less than 15) and with limited drug exposure (drug doses are much lower than those used in Phase I clinical trials). [36] In phase 0 trials the drugs with wider therapeutic index can be evaluated pharmacodynamically (PD) if the agent inhibits the intended target, and the drugs with narrow therapeutic index can be evaluated pharmacokinetically if they achieve adequate drug levels. The phase 0 trials can decrease the total cost of drug development in a significant manner because the failure rate of a new oncology drug is about 90%. [33] Recently published recommendations on the development of phase 0 (Zero) clinical trials from the task force on the Methodology for the Development of Innovative Cancer Therapies (MDICT), have eloquently explained the methodology to conduct phase 0 trials. [37] The problems of phase 0 trials are poor recruitment of patients because of lack of therapeutic benefit, and the development of strong PD markers before the start of phase 0 trials is cumbersome and expensive.

The concept of phase 0 trials is encouraging for pharmaceutical industries in developing countries because of the significant decrease in the total cost of new drug development.
If successful in Oncology drug development, phase 0 trials can open new horizons for developmental therapeutics in other fields of Internal Medicine also.

**Need of Phase “0”**

"Phase Zero" That's what they're calling a recent trial of an anticancer drug from Abbott (ABT-888), which was tested in humans before any safety dosing (Phase I) had been done.

So, how exactly can you do that? By giving extremely small amounts of the drug, that's how, and looking to see if can detect a change in some marker for eventual efficacy. In this case, the marker was inhibition of the activity of PARP, poly(ADP-ribose) polymerase, which is involved in the cellular response to DNA damage. Inhibiting it should make cells much more likely to die once such damage had been detected, which one of many such signals that cancer cells tend to ignore under normal conditions. Abbott's drug seemed to do the trick, so work on it will continue. [38]

The good part of this is that the drug got into humans more quickly than usual, and that its mechanism of action has now been verified (to a first degree of approximation, anyway - it hits the target). This should make a company a bit more confident about moving on to larger trials, and could potentially weed out losers early in the game.

But there are bad parts, too. For one thing, the patients in a phase zero trial have no hope of benefit from the drug: the dose is just too small. The small doses could give results that (for better or worse) aren't relevant to the later real-world ones, too. Another problem is that reliable biomarkers are thin on the ground despite great sums of money being spent to find and validate them. If you're going to let the future of your drug ride on one of these trials, you'd better be confident that you know what it's telling you. What would be worth knowing is how many drugs fail because of lack of effect on their intended target, as opposed to those which hit the target but still have no effect. You'd also want to know: of that first group, what portion are going to be amenable to robust biomarker studies. Those two fractions would tell you how much of an impact this whole idea will have. Right now, I think the error bars are way too large to make a prediction. [39]

**Phase 0 Clinical Trials: An Answer to Drug Development Stagnation?**

"Innovation or Stagnation: Challenges and Opportunity on the Critical Path to New Medical Products," the agency stated that spending for new development of novel therapies had disproportionately increased relative to major drug and biologic product submissions. The investment required for one successful therapeutic launch increased more than 55% in less than a decade, due in large part to the monies required to take a drug from the laboratory and carry it through the clinical phase I to fill trials required for filing and drug launch—the steps between discovery and approval known as the critical path. As a result of the significant escalation in investment required to navigate the critical path, there was great concern about a new health care crisis: a few commercially available products would be required to carry the financial burden for many product failures. [40] The FDA concluded that something was significantly wrong with the critical path. The tools of development had not kept pace with the tools of discovery. To overcome stagnation in the critical path, they recognized that new and practical tools needed to be developed. The only way to meet this challenge was to create innovations in the drug development network to make the process more efficient, effective, and more likely to result in safe products that benefit patients. Out of this statement came the concept of exploratory investigational new drug (IND) studies. Exploratory IND studies are clinical trials conducted early in phase I (hence, the term phase 0) that involve limited human exposure and have a therapeutic or diagnostic intent.2 The purpose of the phase 0 study is to aid in the go versus no-go decision-making process of a drug's fate earlier in the development process, using relevant human models instead of relying on sometimes inconsistent animal data, thus helping to confirm end points such as mechanism of action, pharmacology, bioavailability, pharmacodynamics, and metabolic microdose assessments. These studies of novel agents expose a small number of patients (perhaps 10 or fewer) to a limited duration (eg, 7 days or less) and dose (in the range of one 100th of the dose required to yield a pharmacologic effect of the test substance with a maximum dose of _ 100 _g).3 They are conducted before the traditional phase I dose-escalation safety and tolerance studies. In early 2006, the FDA published "A Guidance for Industry, Investigators, and Reviewers for Exploratory IND Studies" as part of the agency's critical path initiative to streamline drug development and improve the understanding of drugs early in the clinical process.3 There must be several considerations before initiating a phase 0 trial, given that not all novel agents will be appropriate for pre-Phase I analysis. For example, if researchers are to evaluate a specific pharmacodynamic target, they must be certain that the drug's mechanism of action is defined by that target to avoid misleading or even meaningless results. Sorafenib (BAY 43-9006), for instance, was originally tested in clinical trials as a B-Raf kinase inhibitor, but may actually have positive inhibitory effects due to other off-target effects.4 If the clinical investigators of sorafenib had focused solely on B-Raf as its target, the antitumor profile of this drug may have gone undefined. [41] To evaluate target effect, a biomarker must be known and an assay to measure it must be developed and validated before study initiation.6 It is imperative that the sponsor have a biomarker and an assay to use in the Phase 0 trial, and that it is being used, that it gives meaningful results relative to the tissue/organ target of attack. The ethics of doing phase 0 trials must also be considered carefully. 7 These trials have no therapeutic intent and often will require significant invasive procedures. They have a finite treatment duration and, theoretically, are not in the range of efficacious dosing. Fewer toxicity data are necessary, so there is some concern that this limited toxicology will be insufficient and not well defined in every drug scenario to maximize patient safety. [42] **Limitations**

Clinical trials are not infallible, as they only test a small proportion of the target population. If a safety event only happens in 1 in 20,000 people, it may not get picked up during the clinical trials, if only 10,000 people are tested. However, they are the best system we currently have for getting clues as to how safe a treatment is and how well it works, and are better than having no information at all or anecdotal evidence that is hard to piece together.

As techniques get better, and more is known about the body, scientists are increasing the number of drugs and models to predict whether or not a drug will work or be safe, before it is used in humans. However, they will never be able to completely replace clinical trials, and there will always need to be people willing to volunteer for us to learn more about the medicines and treatments for the future. [43] **CONCLUSION**

As there was, until date, not much information on how patient organisations are actively involved in clinical trials and research we have decided that the title of this survey should be the identification of good practices rather than best practices. **REFERENCES**

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