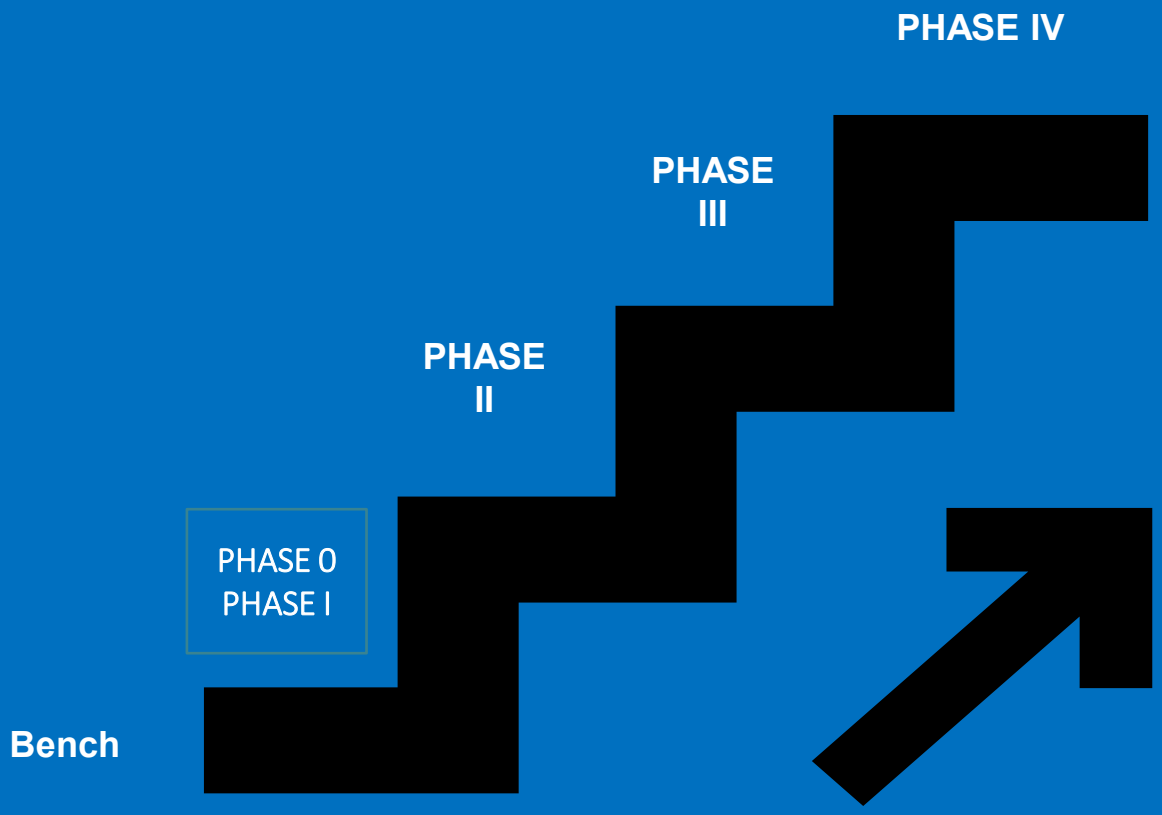
Stages of Research



Stages Pre-Clinical to Phase IV

What percentage of compounds that enter clinical trials will fail?

1.50%

2.25%

3.95%

4.75%

Answer: 95% of compounds that enter clinical trials will fail. A compound is NOT a medication/drug until it is approved by the FDA. Until approval these are test articles, Investigational Product, or compounds.

Stages Pre Clinical to Phase IV

On average how many years dose a compound a compound take to move from the lab to the FDA for consideration as a New Drug Application [NDA]?

1. **1 to 5 years**
2. **6 to 8 years**
3. **8 to 13 years**
4. **13 to 20 years**

Answer: The average time is 13 to 20 years. There are several initiatives to decrease the amount of time from bench to pharmacy.

Bench

Pharmaceutical bench or pre-clinical research is conducted in both academic and pharmaceutical companies. The current example of collaboration:

mRNA technology that has enabled the rapid development of COVID vaccinations. The mRNA technology has been in development for well over a decade.

Bench

Physicians who work in clinical research have no need of any bench research experience.

1. **True**
2. **False**

Answer: False. Many physicians who go on to work in clinical research started as research assistants during their undergraduate and medical school. Physicians may have a dual degree Phd, MS and MD as researchers.

Bench

Which of the following medications was developed by a pharmaceutical company without collaboration with academia?

1. **Penicillin**
2. **Insulin**
3. **Pregabalin**
4. **Pemetrexed**

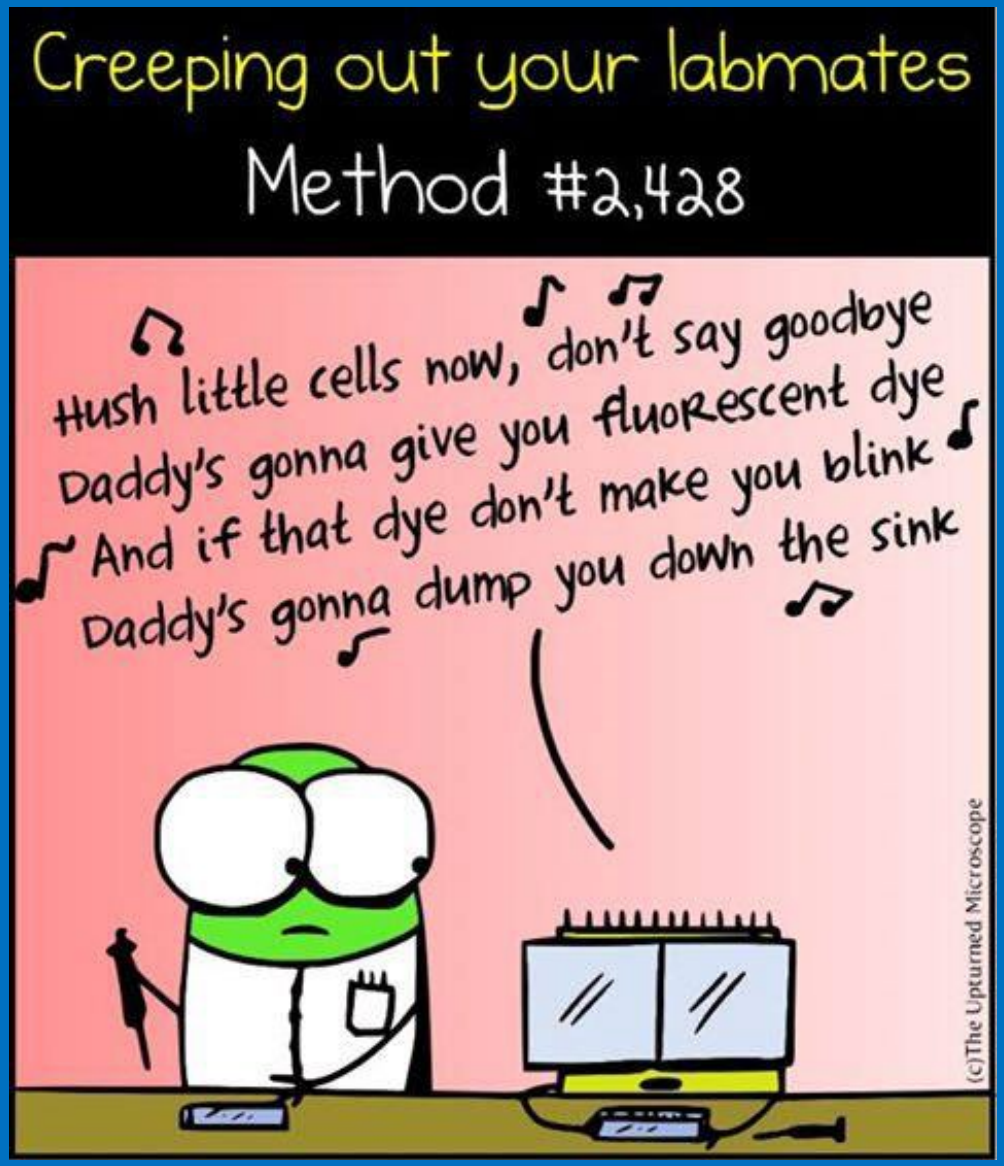
Answer: Insulin was developed by Eli Lily and lead to decades long bench and animal model research in diabetes by the company. Pregabalin and Pemetrexed are examples of medications that all bench research was done in academic labs.

Bench

Bench/pre-clinical research results are predictive of clinical safety profiles and efficacy.

1. **True**
2. **False**

Answer: False, bench/pre-clinical research are poor predictors of safety profiles even with the best of animal models, and efficacy.



Bench

A sense of humor and patience comes in handy for doing research.

Bench

Collaboration between pharmaceutical companies [Sponsors] and academia has decreased over the past quarter of century?

1. **True**
2. **False**

Answer:

False as research has become more complex, the collaboration between academia and pharmaceutical companies has increased. Notably Roche and Genetech, Genomics Institu fo the Novartis Research Foundation located near Scripps Research Institute, Boehringer Ingleheim has established ongoing relationship with Harvard Medical School to initiate mRNAi screening programs. Pharmceutical companies are known in clinical research as Sponsors.

Phase 0

A Phase 0 clinical trial was introduced in 2006 in an effort to modernize and speed up the development of new oncology treatments. It is being expanded to develop treatments for rare and orphan diseases.

This concept was a joint effort of the FDA and the Pharmaceutical Research and Manufacturers of America [PhRMA].

Fewer pre-clinical trials are required if a Phase 0 trial is proposed and accepted by the FDA. Either healthy volunteers or occasionally in Oncology diseases the statistically minimal number of volunteers to prove safety are given less than 1% of the proposed therapeutic dose of the Investigational Product [IP], a microdose.

The duration of such trials is no more than seven days, to minimize the risk of toxicity.

The objective is to facilitate the speed of development of new drug applications [NDA] by eliminating ineffective compounds more quickly.

Phase 0

Which of the following disorders would potentially be considered for a Phase 0 trial?

1. **Stage IV Breast Cancer**
2. **Major Depressive Disorder**
3. **Diabetes Mellitus II**
4. **Fibrodysplasia ossifications progressive [FOP], Stoneman Syndrome**

Answer: 1 and 4

Even though Breast Cancer is the most common cancer in woman, it is a fatal illness with few available treatments.

Stoneman Syndrome is an extremely rare disorder where connective tissue transforms into tendons, muscle and ligaments ossify into bone.

Phase 0

Phase 0 clinical trials are always conducted in an outpatient setting.

1. **True**
2. **False**

Answer: False, as a Phase 0 is a first in human dose and these trials take place with limited animal data they are invariably conducted as inpatients and usually in large institutions.

Phase I

Historically the focus of Phase I clinical trials, first in human, is to demonstrate that the compound, Investigational Product [IP], test article can be safely given to humans at the maximum tolerated dose [MTD]. Efficacy is usually not the primary outcome measure.

Phase I

In Phase I trials only, healthy volunteers are enrolled.

1. **True**
2. **False**

Answer: False, oncology trials, rare disease states, and IP targeting specific organ disease [cardiomyopathy, hepatic cirrhosis] will enroll subjects who have the disease under study [DUS].

Phase I

Which of the following would you expect in a Phase I trial?

1. **Liver Function Assessments, CBCs, Chemistry labs, ECGs**
2. **Pharmacokinetic [PK]**
3. **Hepatic biopsy**
4. **All the above**

Answer: All of the above. To assess safety, the primary outcome of a Phase I trial, participants may have daily or even more frequent laboratory draws, ecgs, and vital signs. PK's are frequently done as part of Phase I trials to assess the Cmax and half life of the IP.

Hepatic or other end organ biopsies or scans such as ultrasounds, are used to assess IP effect as a screening diagnostic tool.

Phase I – Pharmacokinetic

Determining the IP pharmacokinetic profile usually starts but does not end with the Phase I trial.

Pharmacokinetics looks at the movement of the IP throughout the body, regardless of the method of delivery.

PK data may be collected across age groups, gender, racial and ethnic groups, in addition metabolic or degree of hepatic and renal impairment subgroups of PK data may be obtained.

At the conclusion of collecting all the PK data the roller coaster ride an IP takes through the body should be well understood.

Phase I – Pharmacokinetic

Pharmacokinetics profile IP or medication is comprised of four processes:

1. **Absorption**
2. **Distribution**
3. **Metabolism**
4. **Excretion**

Phase I - Pharmacokentics

In the food absorption aspect of a Phase I trial what factors are considered?

1. **The time of dose to the time of ingestion of food.**
2. **The fat content of the meal.**
3. **The caloric content of the meal.**
4. **All of the above.**

Answer: 4, The food effect on oral medications is critical. In phase I trials very specific caloric content, fat content, carbohydrate level are investigated. The classic example is Synthroid, clinical research revealed that Synthroid is poorly absorbed in a non-fasting state.

Phase I - Pharmacokentics

In Single Ascending Dose Studies [SAD] which of the following are false?

1. **Multiple dose levels are used to determine the maximum tolerated dose [MTD].**
2. **Elimination half-life is important to calculate.**
3. **In the US females must always be included in SAD studies.**

Answer: 3, in the US females must be included if there is sufficient pre-clinical data that indicate that it is safe to include female. The primary goal of a SAD trial is to determine the MTD. Elimination half-life is critical as if the IP has a short half life it will need to dosed more frequently.

Phase I - Pharmacokentics

In Multiple Ascending Dose [MAD] which of the following are true?

1. **Placebo control group is not necessary.**
2. **Females are not included due to safety concerns.**
3. **MAD studies are done prior to SAD studies.**
4. **The objective is to determine if multiple doses are safe and tolerable.**

Answer: 4. In SAD and MAD trials placebo groups may be utilized to blind both participants and staff from assuming that adverse events [side effects] are due to the IP. In the US, MAD studies are done after SAD studies and females are included.

Phase I – Pharmacokinetic

Hepatic/Renal Impairment studies are part of many Phase I programs.

Specific groups of renal insufficiency grouped by creatinine clearance and eGFR are matched by age, biologic sex, weight or BMI to a healthy control.

Hepatic impairment is calculated by the Child-Pugh score; hepatic biopsy and/or ultrasound may also be used for classification. As above each hepatically impaired participant is matched to by age, biologic sex, weight or BMI to a healthy control.

PK profiles of the afflicted groups are compared to their matched healthy controls to determine if a dose reduction or increase needs to be considered for the renal or hepatic impairment groups.

Phase I - Pharmacokentics

If a site has been selected to do a Phase I Hepatic or Renal safety trial including pharmacokinetic profiling, then the site must also agree to the healthy volunteer group.

1. **True**
2. **False**

Answer: False, some sponsors may request that a site only be involved in the hepatic and/or renal impairment participant group. Other sponsors may wish for the entire trial be done at one or more sites. Usually these trials are small, conducted at a few sites, usually under six and are brief in duration.

Phase I

Phase I trials are always conducted in inpatient settings.

1. **True**
2. **False**

Answer: False, there are occasions where a Phase I trial may enroll outpatients. An example would be a Phase I trial for children, where the IP has been either FDA approved for adults or is in a late phase trial for adults. A safety and PK finding trial may be conducted with outpatients if and only if the safety data supports this decision.

Phase I

Which types of dose modalities may be used in Phase I trials?

1. **Intrathecal**
2. **Intravenous**
3. **Oral**
4. **All of the above**

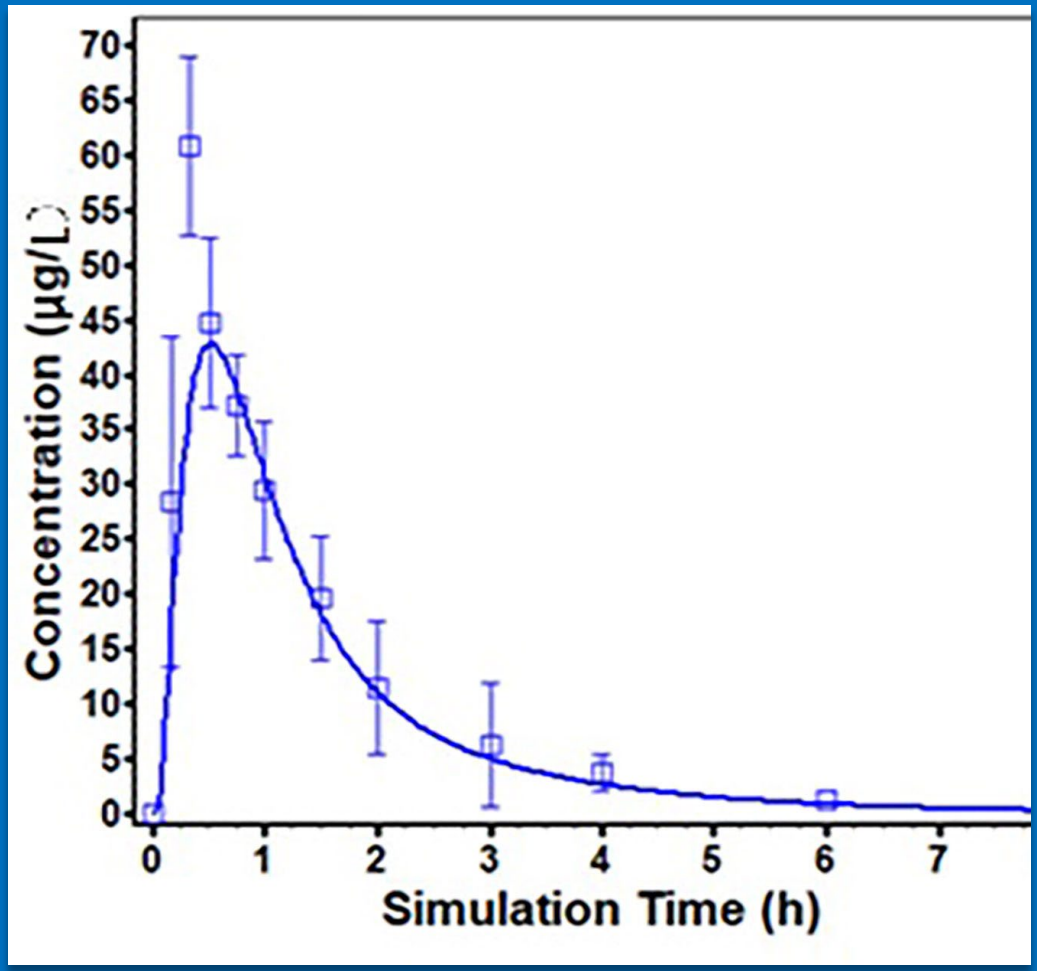
Answer: All of the above. One goal of a Phase I trial may be to compare dose modalities, intravenous to intrathecal or intramuscular to subcutaneous. Sometimes these trials are classified as Phase Ib, because some safety data has been collected in a Phase Ia.

Phase I – Pharmacokinetics

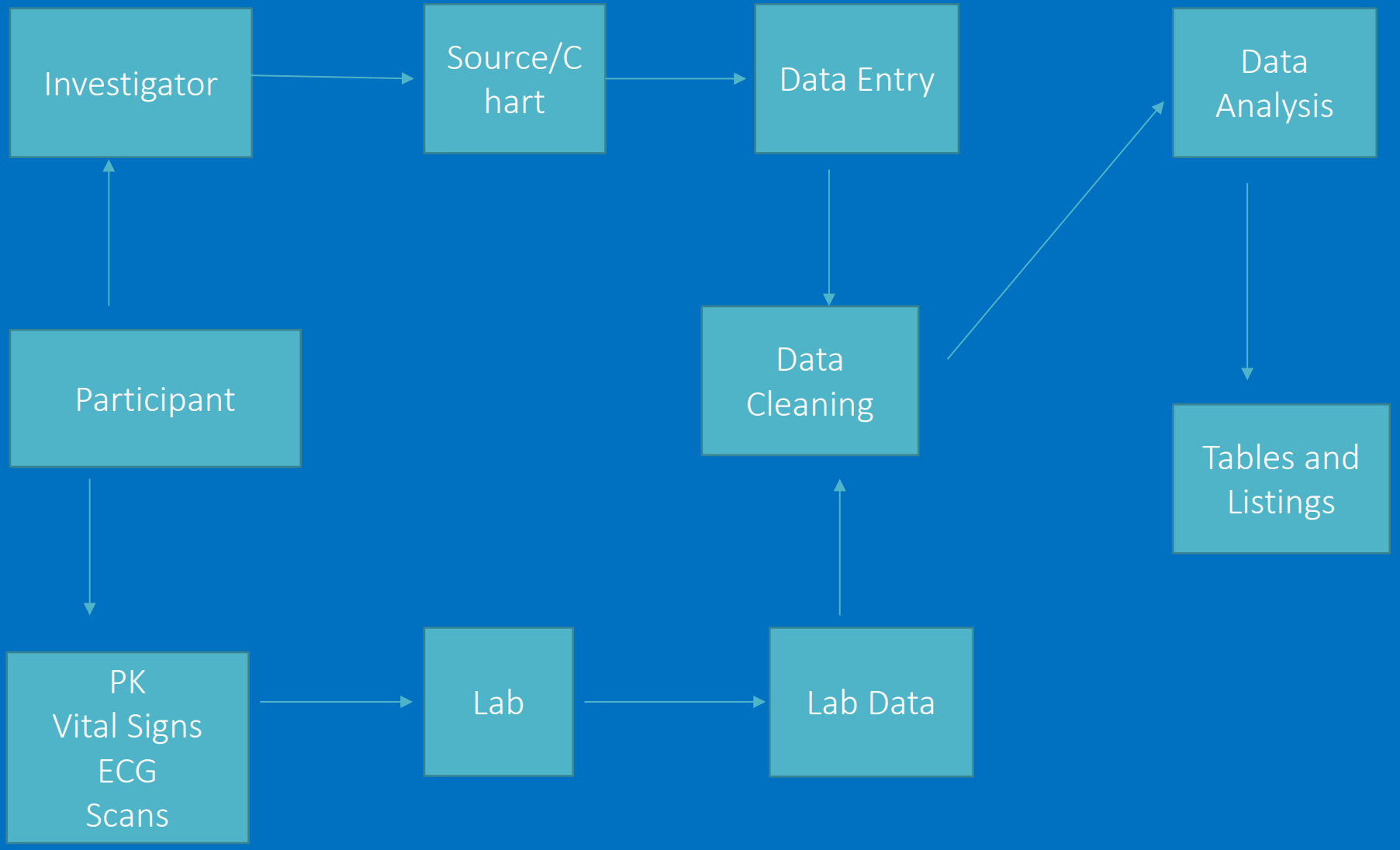
After completion of the Phase I trials the IP profile has been determined ….

Cmax – mean time to peak exposure

Total exposures, AUC [area under the curve]



Phase I Overview



Phase I – Tables and Listings

- Pharmacokinetic data
  - MTD
  - Start of Pks in healthy, hepatic, renal
  - Pediatric or other special population PK data
  - Elimination Half Life
    - *This determines the frequency of dosing*
- Nascent safety event listings
- Route of administration
- Initial dose considerations for the next phase

Phase II

Phase II

For every ten Investigational Products that enter a Phase I only one is deemed sufficiently safe at the MTD, understood regarding the pharmacokinetic profile, and there is a potential indication or Disease Under Study [DUS].

Phase II trials continue to ascertain safety data and pharmacokinetic data in a well defined and tightly monitored participant population.

The goal of a Phase IIa/IIb trial is to collect data on dosages, IP metabolism, safety and efficacy in a particular DUS.

Phase II

Which of the follow are true about Phase II clinical trials?

1. They are always done with outpatients.
2. PKs are usually not part of the procedures.
3. These trials are double blind/placebo controlled.
4. Many different research sites may participant.

Answer: 4, Usually Phase II trials are conducted in many different research sites in the US and the rest of the world [ROW]. Distributing sites globally allows for a diversified data collection across gender and racial groups as well as geographic regions. For example, MS is well known to occur more commonly in northern areas but is there a difference in the IP response across geographic regions. To answer this question, multiple sites are usually used.

As the IP moves into work with participants who have the DUS, different populations, age groups, and the trials move from a few sites to many considerations become more complex.

Phase II

Answer: Many Phase II trials are outpatient; however, if the DUS is a form of cancer, sepsis, status epilepticus, acute psychosis for example the sponsor may elect to conduct the Phase IIa trial in an inpatient setting for patient safety.

Data Safety Management Committees [DSMC] are composed of experts in clinical management of the DUS, pharmacists, statisticians, and others. The DSMC may be blinded or unblinded as to who is receiving IP in the study. Their task is to assess data integrity and safety at pre-determined and ad hoc time points in the time line of the study.

The DSMC may recommend changes in the study protocol, including stopping the study due to safety concerns or moving from an inpatient to a partial or full outpatient setting.

Phase II

Answer: PK collection is frequently part of a Phase II trial as Phase I trials are conducted in a tightly controlled participant group. Phase II trials are conducted in individuals who have the DUS; PK analysis is imperative.

As medical science has advanced there is an increased understanding of the variability in metabolism across individuals who have the DUS and the healthy normal or even specifically hepatic/renal impairment population.

For example, individuals with schizophrenia have a greater risk of metabolic syndrome with impaired glucose metabolism compared to age, gender, racial/ethnic matched healthy individuals.

Phase II

Answer: In general Phase II trials are double blind/placebo controlled. The purpose of the double blind is to assure that the IP is measured on its own merits.

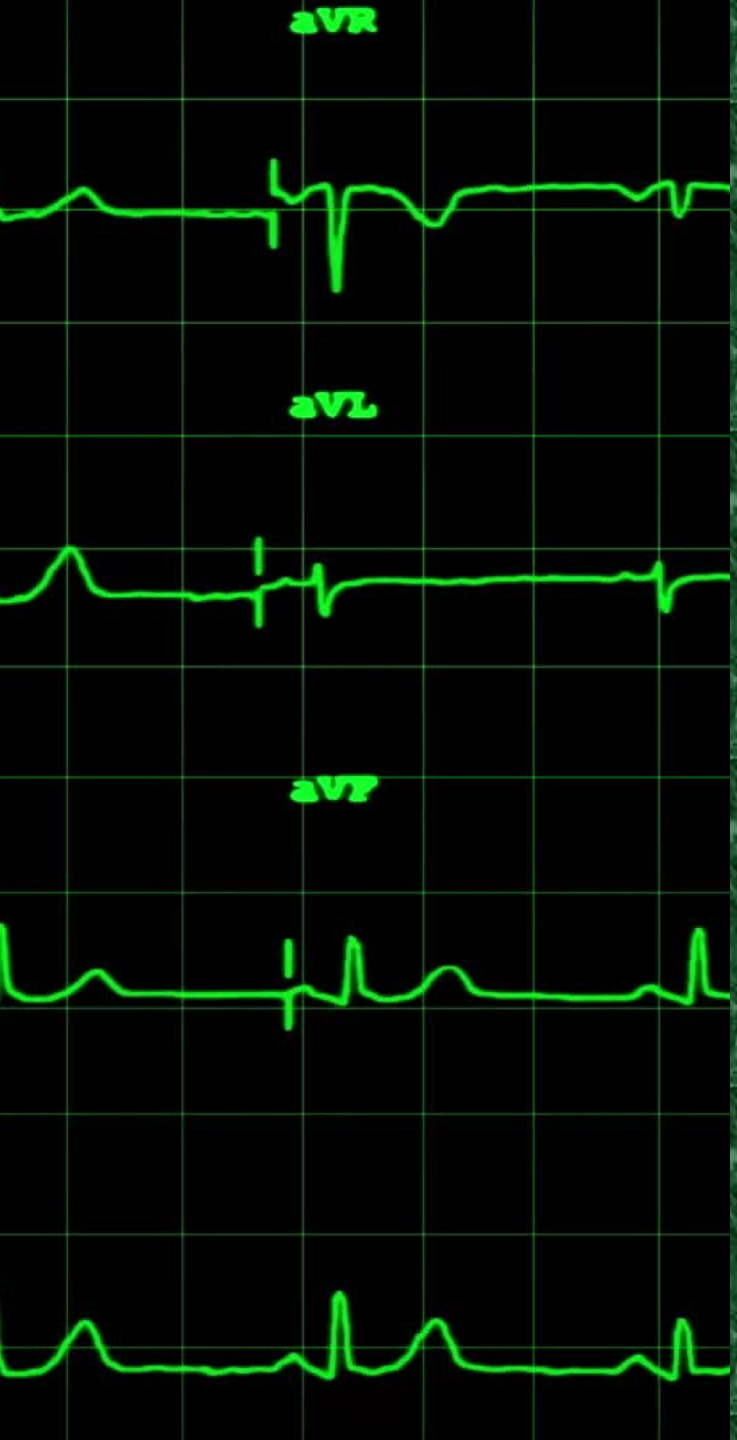
In some DUS a Sponsor may have an Open Label [OL] Phase IIa trial due to the severity or fatality of the DUS. An example would be ALS, severe sepsis, status epilepticus. These OL Phase II trials are conducted as extensions of Phase I trials. If the results of the OL Phase II are sufficiently efficacious and the safety profile acceptable then for the FDA a double blind/placebo-controlled Phase IIb trial is usually conducted.

Phase II

Which is true about Phase II trials?

1. Laboratory results are always part of the trial.
2. ECGs are usually part of the trial.
3. The clinical trial may last one day to several months for an individual participant.
4. All of the above.

Answer: All the above. Collection of safety data [complete metabolic profiles, HgA1c, hepatic profiles, complete blood cell count with differential, urinalysis, pregnancy [serum/urine], urine drug screens, ETOH screen] in addition to any particular laboratory tests that were noted to be remarkable in the Phase I trial are collected throughout.



Phase II

ECGs are frequently part of a Phase II trial. ECGs may be collected in single or triplicate depending on the findings from the Phase I trials.

The PI is expected to interpret all laboratory and ECGs, determining if there is any participant safety risk. The PI is expected to review the data, sign and date the resulted laboratory and ECG tracings.

Phase II trials may have a single visit, such as a genetic or particular laboratory analysis study or may last for several months.

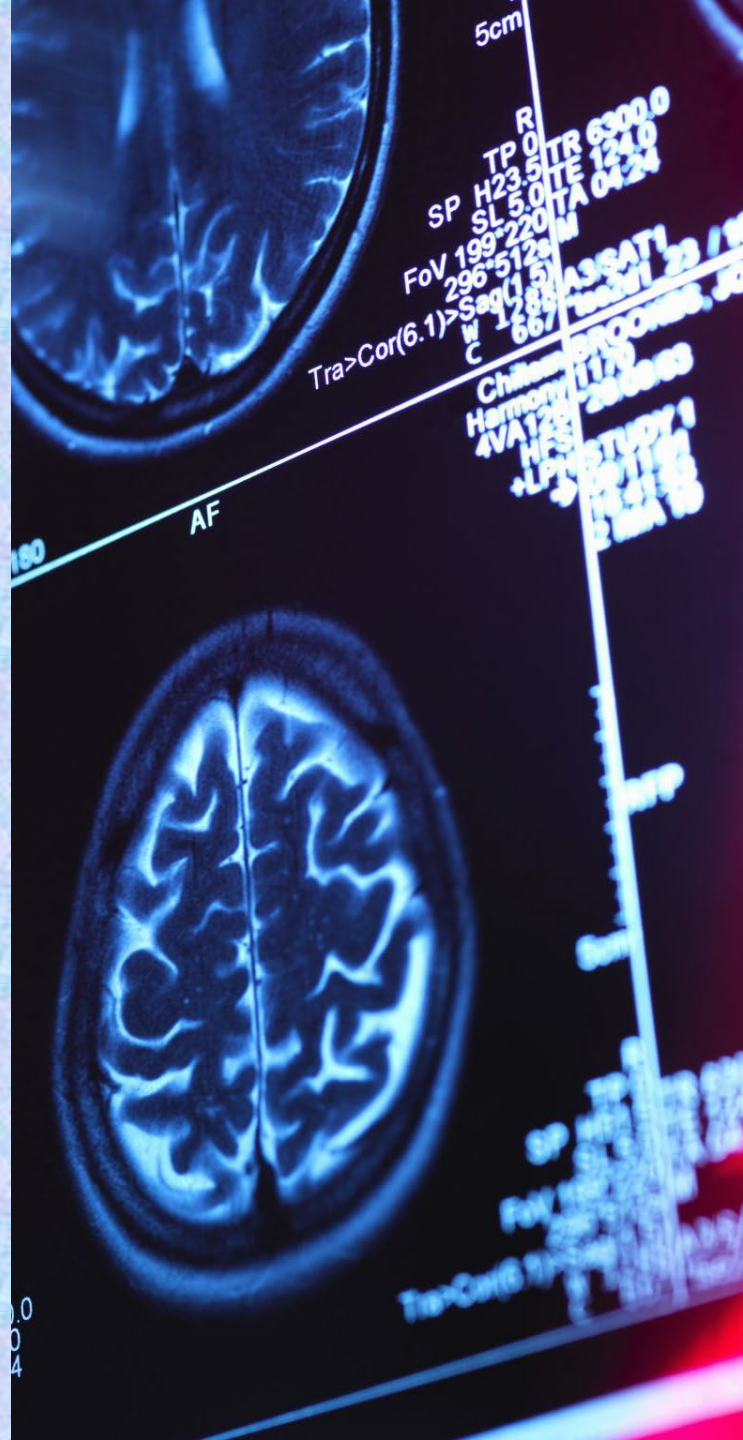
Phase II

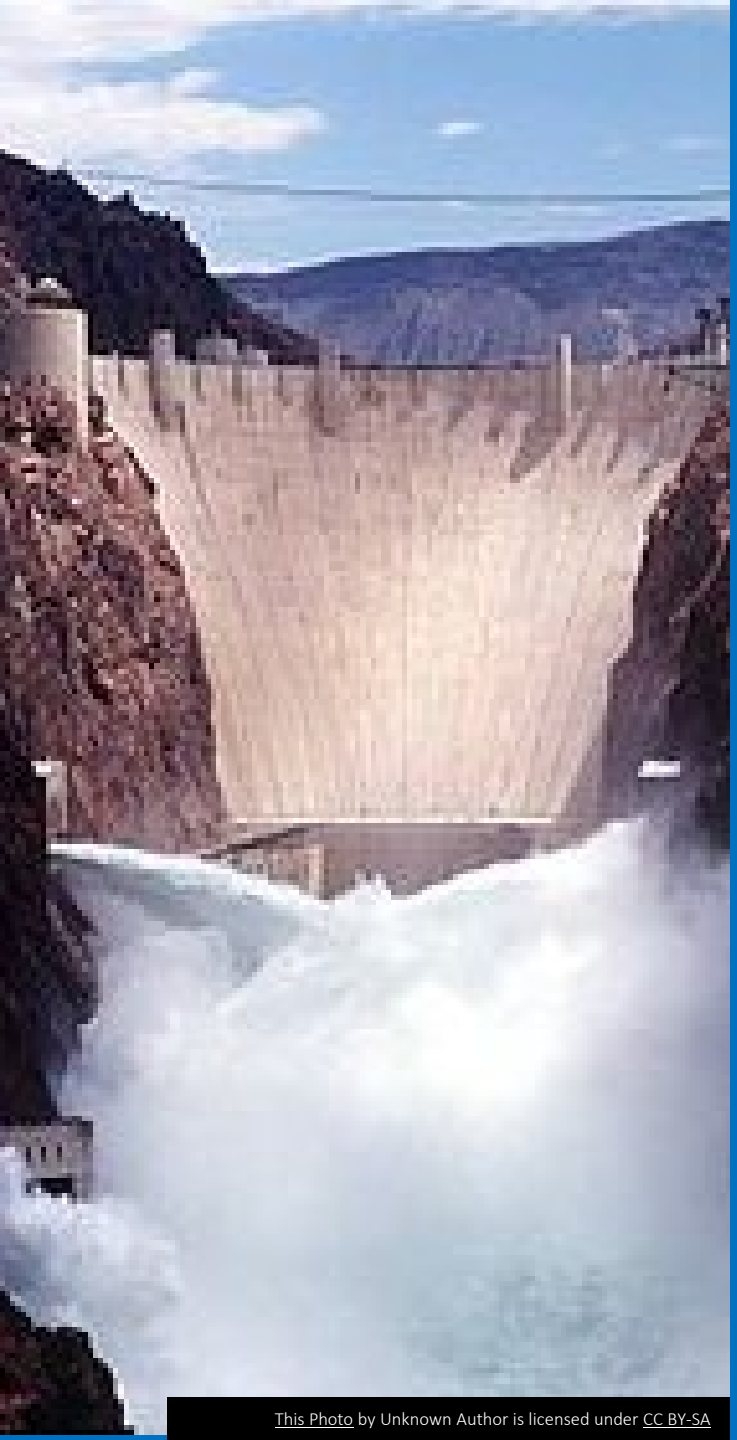
What other data may be collected in a Phase II trial?

1. MRIs/CTs/Ultrasound
2. Tissue biopsy
3. Pharmacogenetic
4. All of the above

Answer: All the above. Depending on the DUS various scans may be used to measure change in disease progression. Tissue biopsies are commonly used in immunologic and oncologic research.

Pharmacogenomic research and data collection has become nearly routine in clinical research. Like PK collection, pharmacogenomic collection is carried forward as the IP progresses.





Phase III

Phase III trials include a broader range of participants with the DUS.

The goal is to determine safety and efficacy of the IP when the proverbial flood gates are carefully opened.

Phase III

Which is true about Phase III trials?

1. Laboratory results are always part of the trial.
2. ECGs are usually part of the trial.
3. The clinical trial may last one day to several months for an individual participant.
4. All of the above.

Answer: All the above. The overall structure of a Phase III trial frequently mirrors its Phase II predecessor.

Phase III

Which is not true about Phase III trials?

1. **There is an open label extension.**
2. **Only adults may be enrolled.**
3. **Safety laboratory, ecgs and other tests are part of the trial.**
4. **The sample size is about the same as a Phase II**

Answer: 1, 2, and 4.

If there is sufficient safety and efficacy evidence from the Phase II trials some sponsors may elect to have an OLE as part of their Phase III program. This allows the collection of additional longer term safety data prior to a regulatory submission.

Phase III

Answer:

The age range for enrollment in a trial is set by the inclusion criteria. Infants, children, adolescents, adults, and elderly may all participant in a clinical trial if this is the intention of the trial. Age of participation is usually captured either at the screening/V1 or randomization visit.

The sample size of Phase III trials is 2 to 5 times that of a Phase II trial. The sample size is determined by mathematical algorithms as to what will be the necessary number of participants to achieve a set confidence limit for statistical analysis. The sample size takes into account the number of individuals who leave the trial prematurely and who do not receive the first dose of IP.

Phase III

What percentage of the compounds move from Phase II to Phase III?

1. **10%**
2. **30%**
3. **50%**
4. **70%**

Answer: 2, approximately 30% of IP's are deemed sufficiently safe and effective to move forward from a Phase II trial.

Phase III

How long does it take a sponsor to complete a Phase III program?

1. **Six to nine months**
2. **One to two years**
3. **Two to ten years**
4. **One to Four years**

Answer: 4, From the time the first patient initiated [FPI] to the completion of the Clinical Study Report [SCR] the compilation of all the data is one to four years on average.

Phase III

What percentage of Phase III trials are positive, that the IP is efficacious?

1. **< 10%**
2. **< 20%**
3. **< 30%**
4. **< 40%**

Answer: 3, Less than 30% of all Phase III trials will result be found positive. This percentage has been declining across all indications for the past 25 years.

Phase III

If there is sufficient evidence that the IP is efficacious for the DUS, is well tolerated, with an acceptable safety profile the IP may be submitted to the FDA as a New Drug Application [NDA].

Phase IV: The sunrise after the IP is now a medication

Phase IV Clinical Trials

Phase IV trials are conducted after an Investigational Product has completed regulatory review [FDA, European Union, UK Health, etc]. The IP is no longer experimental for the population that has received approval, eg individuals over 18 to 65 years of age XX approved to treat acute asthma exacerbation, the IP is now a medication.

When a compound is presented to the FDA for approval the process is termed a “New Drug Application” or NDA. Approvals are narrow and are only apply to certain age groups, genders, level of disease state [eg Stage I Breast Cancer], and for a set duration [usually the duration for which there is safety and efficacy data as measured in the Phase 1 to 3 clinical trials].

In the clinical practice of medicine, we may write a prescription for a patient whose demographics and/or disease state is outside the scope of the FDA approval, known as “off label” prescribing.

Phase IV Clinical Trials

The objectives of Phase IV trials are to study the compound in broader patient groups:

Age Groups – children [defined as birth to 11 years], adolescents [12 to 17 years], Elderly [over 65 years]

Variants in disease state – more advanced cancer, more frequent seizures than originally studied

Duration of exposure – Less frequent adverse events, may not be captured in the relatively short duration Phase I, II, III trials and the population size in the early phase trials may not be sufficient to capture the rare adverse events

Patient complexity – In Phase I to III trials patients with multiple illness/disorders are usually excluded for their safety and the inability to analyze data with confounding variables. In Phase IV open label trials these patients are intentionally included. This allows these medically vulnerable patients to receive cutting edge therapies while we closely monitor the effects of the new treatments.

Phase IV

Which of the following are true in Phase IV trials?

1. **Open label, everyone receives IP**
2. **Variable dosing for an individual subject may be part of the study**
3. **Fixed dosing of IP**
4. **Subjects may self adjust their IP dose**

Phase IV

Answer: 1, 2, and 3. Phase IV trials are usually open label [OL] they may be variable dose or fixed dose.

IP adjustment even in an OL trial requires at the minimum for the subject to contact the site staff. In general IP may be adjusted either at a regularly scheduled visit or an unscheduled [UNS] visit, as per protocol.

Phase IV

IP compliance is not important in Phase IV trials.

1. **True**
2. **False**

Answer: 2, IP compliance is a critical element of all phases of clinical research.

Noncompliance with treatment in medical practice frequently leads to disease progression and/or increase frequency of side effects.

In clinical research noncompliance with IP leads to poor data, decrease in understanding of the efficacy/efficaciousness of the IP, and confusion as to Adverse Events.

Phase IV

Which of the following is/are not generally true in Phase IV trials?

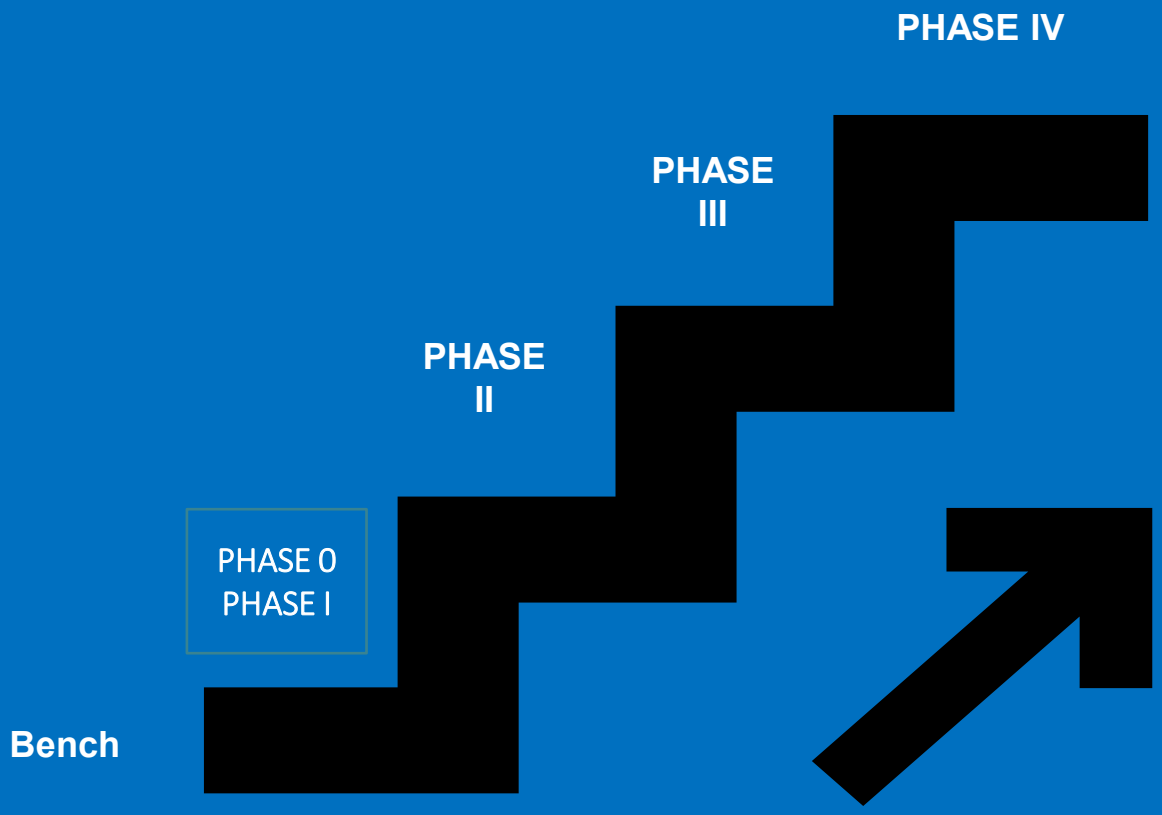
1. **The sample size is relatively small, 10 to 500**
2. **The task is to determine pharmacokinetic profile of the IP**
3. **AE's are not well delineated**
4. **The duration of the trial maybe two to three visits**

Phase IV

Answer: 1, 2, 3, 4 are generally not true in Phase IV trials.

1. The sample size is relatively small, 10 to 500
    1. The sample sizes may well be over 1000 to assess relatively rare AE's
2. The task is to determine pharmacokinetic profile of the IP
    1. Pharmacokinetic profiles are delineated in Phase I to Phase III
3. AE's are not well delineated
    1. A major goal of Phase IV trials is to collect AE's in a broad patient population.
4. The duration of the trial maybe two to three visits
    1. The duration of Phase IV trials ranges from several months to years.

Stages of Research



Congratulations you have completed the first two lectures in the series.
As per your curricula guide, please arrange for a conference call to review the information.