Understanding clinical trials and their outcomes – fake science at its best!

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The term clinical trial is being used often in the scientific literature and recently more so in particular in the public media with regard to developing treatments (e.g. pharmaceutical products, vaccines) for the COVID-19 and its associated pandemic. The term clinical trial is often presented to the public as if it is a form of highly sophisticated science based approach for developing medicines and treatments. Further, it has been implied that clinical trials require higher level of understanding of the complexities of science and financial recourses, which presumably only few developed economies can afford and support. The purpose of this article is to decipher the mystery of clinical trials in simple language so that not only public could understand them but also to provide guidance to the professionals in the area as well.

In simple term, a clinical trial is a form of testing or test where tests are conducted using humans as test subjects for the medicines development, be they are tablets/capsules or vaccines. If the same testing is conducted in animals then it is called pre-clinical otherwise in vitro or laboratory testing (i.e. without dosing humans or animals subjects). A simple example of a "clinical trial" would be a trial/test to see if one gains weight (the outcome parameter) by eating chocolate loaded ice-cream for a month. Such a trial/test can easily be done in home by anyone. What would be required for such a clinical trial, chocolate loaded ice-cream, some human subjects and a weighing scale to monitor the weight (outcome or response parameter) before and after taking the ice-cream (or the so called "dose").

The point, which must be kept in mind, is that a clinical trial is testing to monitor or measure outcome (response) before and after the treatment ("dose"). This means that clinical trials should be conducted under the management of normal/standard analytical (measurement) science or laboratory. If the test products are chemical based (simple or complex) then tests should be conducted in an analytical chemistry laboratory. However, a quick overview of the literature would reveal that most, if not all, clinical trials are conducted under non-analytical chemistry management mostly having medical, pharmaceutical and regulatory expertise. These professions usually have no or limited underlying and required knowledge or understanding of analytical science and/or chemistry of the tested products and/or chemical nature of the body processes. Therefore, it would be safe to assume that most "clinical trials" conducted at present would be of poor scientific authenticity more likely false and useless.

Current practices may be explained with the evaluation pharmaceutical products such as tablet or capsule. It can further be made simpler to understand by considering an example of the development of a generic product vs innovator product.

The idea behind such evaluation is to establish if the generic products are of the same or similar quality, safety and efficacy as those of the respective innovators' products. To establish this, one is required to conduct clinical trials, commonly known as bioavailability and/or bioequivalence assessment, for comparing a

generic product against an innovator's product. That is to conduct testing after dosing the two products separately and measuring and comparing the outcome (response) which in this case is the drug levels of the administered drug. For example, if someone likes to develop a generic version of Tylenol or Advil, then he/she has to administer a Tylenol or Advil against the in-house version of tablet and measures the plasma drug levels which in this case would be acetaminophen or ibuprofen, respectively. Input is tablet, innovator or generic version, and output is plasma drug levels - basically a standard or normal analytical chemistry protocol. However, such studies are conducted under the management of medical and pharmaceutical professionals following regulatory guidance with negligible contribution from chemical and/or analytical sciences for developing study protocol and/or interpretation of the results.

An appropriate analogy to describe the situation or testing would be assessing comparative efficiency of new fuel vs the old one for ships. Ships would be operated following normal or standard protocol, without knowing about the tested fuel manufacturing and testing aspects. Ship will be loaded with new or old fuel at random and will be operated as usual and at the end consumption of fuel be measured and evaluated without involvement of ship caption or crew. If fuel loader and ship operators kept blinded about which ship is getting which fuel, then in technical term the testing/evaluation will be called double blinded.

Similarly, if two medicinal products are to be tested in double blinded "clinical trial" both product administrators and volunteers would be blinded to the tested products. A medical practitioner's role would be just like ship captain to "operate" and monitor normality of the patients or volunteers. A medical/pharmaceutical practitioner would have no or limited knowledge about the manufacturing and/or quality of the products tested and/or their evaluation.

Now let us explore the products evaluation in little further detail. The input part is the tablets or capsules, which for all practical purposes is compressed composite of the drug and some inactive ingredients. This is similar to a candy making process (consider M&M candy) and note that it happens before the tablets/capsules are part of clinical testing. No matter how loudly an argument is made the fact remains that it is a chemical composite candy manufacturing process. Chemical and/or physical tests are conducted to establish the suitability of the tablet/capsule products before administering to human subjects. Once the product is administered, blood samples are withdrawn from human subjects to measure drug levels again in a typical analytical chemistry laboratory or environment. The blood drugs levels are compared to establish similarity of the two tested products following standard analytical chemistry and statistical principles and methods.

Now consider if indeed one is measuring and/or evaluating similarity of the two tested products. In scientific or technical term, one would be measuring mean and variability (variance) of blood drug levels for these two products. If the means and variabilities are the same and similar for both products then products will be declared equivalent and authorities would allow their interchangeability. Question, however, is, is this comparative protocol valid for seeing the mean and variability similarity or differences in the compared products. The answer is certainly no! The reason being, for such a protocol, there are three sets of variabilities contributing to the blood

drug levels i.e. (1) inter and intra products (tablets/capsules); (2) inter and intra human subjects - physiological; (3) blood drug level measurements. It is a well-known fact that most variability in this regard comes from human physiological variations which are not only extremely high but also not possible to control or reduce. Products and drug measurement variabilities are usually small and insignificant and are buried (confounded) in the physiological variability. It is, therefore, not possible to determine accurately variabilities of the products or their quality, which in reality is the main objective of conducting the bioequivalence assessment or the so called clinical trials. It is often assumed that statistical analysis of the data take cares the different variabilities aspects, however, unfortunately this is not an accurate assumption as statistical analysis presumes constant or fix intra and inter subject variability - which is not correct. So what is the use of conducting such testing/clinical-trails – not much! It is important to note that such clinical trials are not only conducted for developing generic products, but also for innovators' products as well. Every time a product is developed such bioavailability assessments of the drugs in humans are required by the authorities and are conducted accordingly.

In short, such studies (clinical trials) are not only scientifically false for the intended purpose, but also give false assurance to public that products are being assessed and approved based on science and/or clinical assessment. Furthermore, unfortunately, participating human subjects, mostly healthy adults, are exposed to unnecessary risk of potent chemicals often labelled as "lifesaving medicines".

Now let us consider the recent vaccine development aspect with the above described clinical trial explanation for assessing safety and efficacy and quality of a vaccine and/or its product. To conduct a study/testing/clinical-trial, as noted above, one is required an input (dose of a vaccine), output (response) and human (patients or healthy subjects treated with virus). Starting with a dose of vaccine – question is, from where this vaccine candidate will come to initiate a clinical trial. The only way a trial vaccine could be developed is if one has access to a virus which the potential vaccine candidate would be capable of killing at least in vitro to start with. However, it is a well-known fact that a reference virus (identified and quantified) is not available, at least in sufficient quantities, then how a potential vaccine candidate would be developed to administer for clinical trials. It cannot be! Therefore, it is impossible to have an appropriate vaccine candidate to conduct clinical trials.

Let us assume that somehow magically a potential vaccine candidate becomes available and ready for dosing to the subjects. Then after dosing what would be the measurable response which one would be monitoring to establish efficacy of the vaccine – presumably immunity to virus and/or its infection. The only way to know about the immunity would be to inject virus to create sickness to see if the created immunity kills virus and/or protect humans from the sickness. However, as stated previously, there is no virus SARS-COV2 available hence immunity against virus cannot be checked and/or established. So, what would these clinical trials be for – obviously nothing! From the science perspective conducting such clinical trials is simply a futile exercise at least at present. However, medical, pharmaceutical and regulatory professionals are promoting and

conducting clinical trials while clearly exposing human subjects to potentially dangerous and potent chemicals. Therefore, the so called "science" of clinical trials should be challenged for its lack of relevance and usefulness on an urgent basis.

At present, medical and pharmaceutical science works on the basis of regulatory compliance, which means meeting regulatory criteria, set mostly with arbitrary or fictional standards and specifications at least from scientific perspective. For example, the compliance requirements of bioavailability/bioequivalence assessment are purely on arbitrary basis as explained above which does not provide any assurance about the quality, safety and efficacy of the tested products. However, authorities would approve the products as safe and efficacious because they (products) meet their (authorities') compliance criteria.

Similarly, in case of vaccine development, there is no possibility of developing an appropriate and valid vaccine as neither a valid reference virus nor a valid test is available to monitor efficacy of the vaccine. On the other hand, authorities would set some arbitrary compliance requirements/standards based on some RNA/DNA monitoring along with some antibodies testing, both mostly nonspecific and irrelevant as described previously. Therefore, if a vaccine will be developed, it will not be assessed and approved on the basis of its killing or neutralizing ability of the virus or curing patients, but based on meeting regulatory compliance requirements mostly unrelated to the virus and/or its associated disease (COVID19).

On the other hand, if one would consider the issue based on analytical or measurement science, not only the issues can be resolved accurately but extremely efficiently and cost effectively.

For example, in case of bioequivalence testing, first of all, such irrelevant and flawed clinical testing is not necessary and should be discontinued immediately from the regulatory requirements. Quality, efficacy and safety of the products (generic and innovators) can easily, accurately and with scientific validity be established with laboratory testing only. It is hard to argue against the use of valid laboratory based testing alone in this regard.

With regard to vaccine, as explained above not only it is not possible to develop an appropriate and valid vaccine – in reality it is not even necessary to develop one. At least two issues to consider in this respect are: (1) presumably vaccines are being developed for a still unknown, or non-quantifiable, virus in humans, so chances of being successful in this regard are almost zero; (2) vaccine is being developed for protection/immunity from future viral attack. What are the chances of coming back of exactly the same virus in future – low to zero? It can be argued that experts in virology, along with epidemiologists, mistakenly claimed or assigned the ownership of the situation resulted in a labelled viral pandemic with a suggested solution to develop and have a vaccine. However, issue clearly belongs to analytical science and chemistry.

If one considers the situation that the world has been attacked by a virus which causes severe acute respiratory syndrome (so the name SARS) resulting in infection which may lead to serious health issues and possibly deaths. Hence logically would it not be more appropriate to treat the infection with typical infection medicines such as

antibiotics. There are suggestions that SARS infections can be treated with antibiotics, however, for some unknown reasons such treatment is neither allowed nor encouraged. If for some reason, it is considered that an improved and/or specific antibiotic is needed, it will be much more efficient and cost effective to develop a new or modified antibiotic. The reason being that the dose (input) would be a defined and well characterised chemical compound (antibiotic) relatively easier to develop and manufacture in large quantities with defined characteristics, output or response would be measurable i.e. changes in infection levels. However, there appears to be a clear mindset that only solution is a vaccine which needs to be developed. Such an approach certainly lacks logic indicating practice of flawed or fake-science. This also indicates that the issue of disease/pandemic and its treatment are in the wrong hands, unfortunately with false assumptions and criteria, because claims are being made for the presence of virus and developing vaccines when in reality trials or studies are about the analytical chemistry or science.

In summary, clinical trials are specific type of tests in which products or treatments are tested using human subjects. Such trials should be conducted under the management of analytical science or laboratory with scientifically valid protocols. Unfortunately, however, at present trials are conducted in non-analytical science facilities and supervision often with invalid study protocols and interpretations. Approved products based on such trials would provide false assurance of safety, efficacy and quality of the tested products. Patients and public should be aware of current flawed scientific practices in this regard. On the other hand, if such evaluations are conducted with appropriate and scientifically valid and proven approaches, one could not only avoid false mishaps but also develop treatments and cure far more expeditiously and cost effectively.

PS: If one requires specific references to the views presented here, they could be obtained by visiting the site (www.drug-dissolution-testing.com) or directly contacting the author at principal@pharmacomechanics.com.