New drug approval probability model in phased clinical trials

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Abstract: Modern medicine brought with it "evidence-based practice", which demands that a diagnostic test or treatment method or drug to be used on humans must be proven to be at least safe and efficacious; and the result from the use of such must be reliable and repeatable. These days, the need for evidence-based practice has become even more imperative. Evidence-based practice extends to veterinary practice and also to non-medical practices, for instance in oil exploration. To satisfy these demands in drug testing, robust statistical methods of assessment and ethical procedure must be employed. We here develop and present a probability model for the approval of a new drug intended for use in man or animal. The model showed that there should be more than one evaluation committee working on the approval of one drug at a time. This approach would help in minimizing the error of approving wrongly drugs that should never have been approved. The proposed method has proven the workability and value of using at least three independent evaluation committees, working with the same sets of criteria, in assessing the basis for the use of a new drug and its approval.

Keywords: Evaluation Committee, Approval Probability, Clinical Trial, New Drugs, Informed Consent

1. Introduction

Most health care professionals want their patients to have the best available clinical care, but the problem there often have is the inability to clearly identify the optimum drug or intervention procedure. In the past, clinicians used their own experience or advice from colleagues to make treatment decisions. Nowadays health professionals tend to rely on evidence-based medicine—the systematic review and appraisal of clinical research findings [1]. This study is aimed to develop and present a probability model for the approval of a new drug intended for use in man or animal. Probability models are statistical expressions aimed at explaining an uncertain situation or circumstance. It is aimed that the model will show that there will be more than one evaluation committee working on the approval of one drug at a time. Drug use in health care is intended to deliver appreciable remedies; however, erroneous approval of a new drug and the use of such drug can result in colossal disaster. Procedure for the approval of a new drug is expectedly a very careful and rigorous task. Erroneous approval of a new drug may result from any point in the methodology adopted; ranging from the layout of drug trial to the eventual statistical model and analysis thereof. Building useful disease-drug-trial models is a challenging task and cannot be optimally achieved by any single organization. It requires coordinated efforts by industry, academia, and regulatory scientists [2].

Clinical trials are conducted to allow safety and efficacy data to be collected for a new drug or device [3].These trials can only take place once satisfactory information has been gathered on the characteristics and quality of the new product. Health authorization and approval is granted in the country where the trial took place if the new drug passed the required approval criteria. Since the trial is designed to test hypothesis, rigorously monitor and assess what happens, it can be seen as application of the scientific method to understanding human or animal biology [4].

Usually before a new drug is approved for use, it is subjected to a series of clinical trials by a number of co-operating Standard Medical Quality Control Bodies initially using test animals and later human subjects[5].Clinical trials are preceded by ethical approval. The mutual co-operating evaluation bodies try to replicate one another's experiment to determine whether or not the results are repeatable and reliable. Positive approval is finally granted by the apex regulatory agency when proportions of subjects improving with the new drug therapy are found to be significantly higher than the proportions improving with the existing or standard drug in all or at least most of the trials on the new drug remedy. Results of clinical trials are required by National Drug Regulatory Authority/Agency to guide decision making in approval for use of a new drug and the safe-dosing thereof. For instance in the United States, before a new drug is approved for the treatment of a specific disease and becomes available for doctors to prescribe, the drug's sponsors (usually a pharmaceutical company) must submit a "New Drug Application" (NDA) to the United States Food and Drug Administration (FDA). The NDA tells the story of the drug's development from laboratory and animal studies through to clinical trials, including "efficacy" trials in which the efficacy and safety of the new drug and of a standard drug for the disease are compared by giving groups of patients the different drugs and measuring several key (primary) "outcomes." FDA reviewers use this evidence to decide whether to approve a drug[1]. The equivalent of FDA in Nigeria for instance is the National Agency for Food and Drug Administration and Control (NAFDAC).

Clinical trial is both experimental and prospective. Participants to be drawn into trials are educated on the details of the trial and informed consent obtained from them. In experimental study, investigators ask participants to take or use a product (such as a drug) or do something (such as an exercise) and what happens to the participants as a result are recorded. In prospective study, investigators follow the participants over a period of time and record the outcome. A prospective study does not rely on reconstruction of past events and generally is considered to results that are as reliable as a retrospective study that relies on historic data. Most clinical trials that involve testing of new intervention procedure progress in an orderly series of steps called phases [6].Clinical trials follow phases of pre-clinical trials on animals.

Phase-I clinical trial: These are the first studies conducted to assess how a new drug intervention works in people, the manner and frequency of its application and if it is a remedy, what dose range is safe for use. Phase-I clinical trial usually enrols only a small number of participants, sometimes as few as a dozen.

Phase-II clinical trial: The phase continues to test the safety of the intervention and begins to evaluate how well it works. This phase usually focuses on a particular disease or condition.

Phase-III clinical trial: This phase tests the new intervention in comparison to existing standard products used in the same disease condition. Phase-III clinical trials often enrol larger numbers of participants and may be conducted by many clinics and health institutions. This phase is usually very reliable as samples size is large and participants' drug idiosyncratic reactions (if any) are more likely to be observed.

These phases of clinical trials are applied to individuals by randomization. Participant randomization is important as it minimizes bias. Here the participants are assigned by chance rather than by choice to either the investigational or control group, preferably matched on some characteristics. This approach is the most reliable way to ensure that participants in the two groups are similar and therefore comparable. Participants assignment can be blinded, which is another way of checking bias[7].This can either be single-blinded trial, where participants do not know which group they belong until the end of the trial or double-blinded, where neither participants' nor investigators know which group participants belong until the trial is concluded.

2. Materials and Methods

We here assume that three mutually co-operating (using the same assessment criteria) evaluation committees' working under a drug regulatory authority/agency have tested a certain new drug, for possible approval and that they may or may not agree with one another's findings. Let A and $\bar{A}$ be respectively the events that the first evaluation committee, x approves and does not approve the new drug for use; B and $\bar{B}$ be respectively the events that the second evaluation committee y approves and does not recommend for approval of the drug for use; and C and $\bar{C}$ be respectively the events that the third evaluation committee z recommends the new drug for approval and does recommend the drug.

Let

The probability that the first evaluation committee x recommends the drug be P(A)=a, the probability that the second evaluation committee y recommends the drug be P(B)=b and the probability that the third evaluation committee z recommends the drug for use be P(C)=c

Also let

The probability that the second evaluation committee, y recommends the drug for use given that the first evaluation committee, x has recommended it be P(B/A)=d, the probability that the third evaluation committee, z recommends the drug for use given that the first evaluation committee, x has recommended it be P(C/A)=e, the probability that the third evaluation committee z recommends the drug for use given that the second evaluation committee, y has recommended it be P(C/B)=f and the probability that the third evaluation committee, z recommends the drug for use given that the first and the second evaluation committee, x and y have recommended it be P($C/A \cap B$)=g.

We assume that these probabilities can be calculated from data on the current clinical trials on the new drug by these bodies or estimated from historical data on similar drug approval performances by the three evaluation committee bodies.

Now

$$P(\bar{A}) = 1 - a, \; P(\bar{B}) = 1 - b, \quad P(\bar{C}) = 1 - c, \quad P(\bar{B}/A) = 1 - d,$$
$$P(\bar{C}/A) = 1 - e \quad P(\bar{C}/B) = 1 - f \text{ and } P(\bar{C}/A \cap B) = 1 - g$$

The combination of recommendation(s) and non-recommendations of the new drug by the three evaluation committees may be presented as an events sample space, S, as

$$S = \{ABC, AB\bar{C}, A\bar{B}C, A\bar{B}\bar{C}, \bar{A}BC, \bar{A}B\bar{C}, \bar{A}\bar{B}C, \bar{A}\bar{B}\bar{C}\} \quad (1)$$

The probability that the three evaluation committees simultaneously recommend the drug is

$$P(ABC) = P(C/A \cap B) \cdot P(B/A) \cdot P(A) = gda = gad \quad (2)$$

The probability that the first evaluation committee and the second evaluation committee recommend the drug but the third evaluation committee does not recommend it is the probability of the event set $S_{xy} = \{AB\bar{C}\}$ which is obtained as

$$P(AB\bar{C}) = P(\bar{C}/A \cap B) \cdot P(AB)$$

$$P(\bar{C}/A \cap B) \cdot P(B/A) \cdot P(A)$$

$$= (1 - g)ad \quad (3)$$

The probability that the first and third evaluation committees approve the drug and the second evaluation committee does not is the probability of the event $S_{xz} = \{A\bar{B}C\}$

$$P(A\bar{B}C) = P(\bar{B}/AC) \cdot P(AC)$$

But

$$P(B/AC) = \frac{P(ABC)}{P(AC)} = \frac{P(ABC)}{P(C/A) \cdot P(A)} = \frac{gad}{ea}$$

So that

$$P(\bar{B}/AC) = 1 - \frac{gad}{ea}$$

Hence

$$P(A\bar{B}C) = \left(1 - \frac{gad}{ea}\right) ea$$

$$= ea - gad = a(e - gd) \quad (4)$$

Also

The probability that none of the evaluation committee recommend the drug is the probability of the event $S_0 = \{\bar{A}\bar{B}\bar{C}\}$ which is

$$P(\bar{A}\bar{B}\bar{C}) = 1 - P(A \cup B \cup C)$$

or

$$P(\bar{A}\bar{B}\bar{C}) = 1 - [P(A) + P(B) + P(C) - P(AB) - P(AC) - P(BC) + P(ABC)]$$

$$= 1 - [a + b + c - ad - ea - bf + gad] \quad (5)$$

The probabilities of the other events in S are similarly calculated and the results are shown in table (1)

Table 1. *Approval Probabilities for the New Drug by the Three Evaluation Committees*

S/N	Events	Approval Probabilities
1	ABC	Gad
2	$AB\bar{C}$	(1- g) ad
3	$A\bar{B}C$	a(e - gd)
4	$A\bar{B}\bar{C}$	a(1- e)- ad(1- g)
5	$\bar{A}BC$	bf – gad
6	$\bar{A}B\bar{C}$	b (1 – f) - ad(1- g)
7	$\bar{A}\bar{B}C$	c - ea - bf+ gad
8	$\bar{A}\bar{B}\bar{C}$	$1 - [a + b + c - ad - ea - bf + gad]$
9	S_2	Approval by at least two evaluation committee ab+ae+bf-2gad
10	S_x	Approval by evaluation committee *x* and at least one of the other two …. …. Ad+ae-gad
11	S_y	Approval by evaluation committee *y* and at least one of the other two …. …. Ad+bf-gad
12	S_z	Approval by evaluation committee *z* and at least one of the other two …. …. ae+bf-gad

If the drug is to be approved if and only if the three evaluation committee simultaneously approves the drug; then the expected probability of approving the new drug is

$$g.d.a = gad$$

If at least two evaluation committees must approve the drug before use, then the required probability of approval is

$$P(ABC) + P(AB\bar{C}) + P(A\bar{B}C) + P(\bar{A}BC)$$

That is $P(S_2)$
= gad + (1- g)ad + a(e-gd) + (bf-gad)
= gad + ad – gad + ae – gad + bf – gad
= ad + ae + bf – 2gad

or

$$P(S_2) = ad + ae + bf - 2gad \quad (6)$$

If there is a supervising body such as the first evaluation committee who must recommend for approval in addition to at least one other evaluation committee before the new drug is considered approved for use, then the required events set is $Sx = \{ABC, AB\bar{C}, A\bar{B}C\}$ and the corresponding probability is

$$P(Sx) = (ABC) + P(AB\bar{C}) + P(A\bar{B}C)$$

$$P(Sx) = gad + (ad - gad) + (ae - gad) = ad + ae - gad \quad (7)$$

If the supervising body is the second evaluation committee who must recommend in addition to at least one other evaluation committee before the new drug is

considered approved for use, then the required events set is $Sy = \{ABC, AB\bar{C}, \bar{A}BC\}$

And the corresponding probability is

$$P(Sy) = P(ABC) + P(AB\bar{C}) + P(\bar{A}BC)$$

$$P(Sy) = gad + ad - gad + bf - gad$$

$$= ad + bf - gad \qquad (8)$$

If the supervising body is the third evaluation committee who must recommend the drug for approval in addition to at least one other evaluation committee before the new drug is considered approved for use by the regulatory agency, then the required events set is $S_z =$

$$\{ABC, \bar{A}BC, A\bar{B}C\}$$

And the corresponding probability is

$$P(Sz) = P(ABC) + P(\bar{A}BC) + P(A\bar{B}C)$$

$$P(Sz) = gad + (bf - gad) + (ae - gad)$$

or

$$P(Sz) = bf + ae - gad \qquad (9)$$

These probabilities are also shown at the bottom of Table 1

3. Illustrative Example

The application of new drug approval probability model using three mutual co-operating evaluation committees *x, y* and *z* working on the quality assessment or evaluation of a new drug for possible approval for human consumption based on phased clinical trials

In a Phase III single blinded clinical trial, three mutually exclusive evaluation committees *x, y* and *z* carried out prospective studies for the approval of a new drug for use by individuals. They each selected random samples of 500 individuals respectively and administered the drug on each of these 500 individuals matched on such characteristics as body weight, age, gender etc. Each of these criteria of administration of the drug together with dosage, duration of treatment and response were recorded in the individual case files and they form the basis for possible approval of the new drug by the co-operating bodies. Based on the individual responses to the drug, the three co-operating bodies arrived at the following probabilities of approving the drug for use as $P(A) = a = 0.10$, $P(B) = b = 0.12$ and $P(C) = c = 0.15$.

Assume peer review using retrospective approach, evaluation committee *y* will study the case files of individuals recommended by evaluation committee *x* and match their own evaluating criteria with that of individuals recommended by evaluation committee *x* and decide to recommend for approval with $P(B/A) = d = 0.20$. Also evaluation committee *z* matched their own criteria for recommendation with those used for individuals recommended by evaluation committee *x* and recommended for approval with $P(C/A) = e = 0.24$. Equally evaluation committee *z* compared criteria of its own recommendation with that of evaluation committee *y*'s and recommends with $P(C/B) = f = 0.26$. Finally, evaluation committee *z* checked the recommended cases by evaluation committee *y* which has already been recommend by evaluation committee *x* to help decide whether or not to recommend and then recommending with $P(C/A \cap B) = g = 0.30$. These hypothesized recommendation rates may under certain circumstances be too conservative or too liberal, but nevertheless they are instructive for illustrative purposes.

Under these conditions the estimated approval probabilities using equations (1) to (9) are as recorded in Table 1 are presented in Table 2.

Table 2. *The Estimated Approval Probabilities for the New Drug by the Three Co-operating Bodies A, B, and C (a = 0.1, b = 0.12, c = 0.15, d = 0.20, e = 0.24, f = 0.26, g = 0.3)*

S/N	Event	Estimated Probabilities
1	ABC	0.0060
2	$AB\bar{C}$	0.0140
3	$A\bar{B}C$	0.0180
4	$A\bar{B}\bar{C}$	0.0620
5	$\bar{A}BC$	0.0252
6	$\bar{A}\bar{B}C$	0.0748
7	$\bar{A}B\bar{C}$	0.1008
8	$\bar{A}\bar{B}\bar{C}$	0.6992
9	S_x(1st evaluation committee and at least one other approval)	0.0380
10	S_y (2nd evaluation committee and at least one other approval	0.0452
11	S_z(3rd evaluation committee and at least one other approval)	0.0492
12	S_2 Approval by at least two evaluation committees	0.0552

4. Discussion

In this paper we attempted to develop a probability model that would help the approving bodies in decision making concerning a new drug, assuming that results of clinical trials of three co-operating quality control bodies form the basis for the approval. It is seen from table 2 that the probability is 0.006 that the three evaluation committees must positively recommend the drug before the drug is used by individuals. This is rather very small and stringent when compared with the probability that at least one or two evaluation committees must approve before the use of the new drug is allowed. This is very important because the use of drug concerns life of either man or animal. If it is required that there should be a controlling evaluation committee supervising other evaluation committees, the probability of approving the drug is as high as between 3.8% and 4.9%. If only one evaluation

committee is required to recommend for use, the recommendation rate ranges from 6.2% to as high as 10.1%. If at least two evaluation committees must recommend the new drug before it is allowed for human use then the expected probability of such an approval will be about 5.5%. Errors in trials and approval decision are often costly. Thalidomide use in pregnancy is a case in point. This drug, an anti-emetic and also a sedative, was discovered during post-market-surveillance to be highly teratogenic. Used in Europe by pregnant women to treat morning sickness because of its unusual 'safety' after extensive testing; despite the high rates of malformations (20-30%) and their characteristic pattern, the teratogenicity of thalidomide was not suspected for years[8]. Thalidomide was the first medicine discovered to be highly teratogenic [9]. The suffering it caused has prompted the belief that every drug has the potential to be a new thalidomide [10, 11].

Some researchers and investors may argue that this current proposal will be costly to implement. However, Collier (2009) reported that economists have assessed the cost of ensuring that a new drug is safe for use is too heavy to bear[12]. Nonetheless, in cutting cost, the system must save humanity from the calamity of failed drug. Governments, corporate bodies and other non-governmental organisations and individuals therefore must be encouraged to support the funding of drug testing.

5. Conclusion

The new drug approval probability model proposed in this work has revealed that using at least three different but mutually co-operating evaluation committees working with same sets of criteria on a particular new drug trial for possible approval will definitely reduce the chances of erroneous approval, thereby ensuring high safety and efficacy in drug use.

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