Assessment of treatment effects in single cases and small groups: assumptions, logic, algorithm, computations

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Statistical approaches toward assessment of the effect of treatment, analyzing large sets of data, are increasingly effective and popular. Nevertheless, in medicine, drug safety, litigation, and many other disciplines, *causal assessment* in *single cases* and *small groups* rather than populations or statistically significant samples, is one of the major areas of operations. Almost exclusively, this employs the methods of qualitative analysis. The attempts of quantification of the causal assessment in these cases pose specific and difficult-to-solve methodological problems. Although an interest toward quantitative analysis of single cases is growing,[2,3,4,5,6,7] the existing approaches, in our opinion, did not reach the level of practical significance in the areas of our interests yet. The emergence of modern analytical approaches and computational techniques motivates our pursuit for a computational approach and algorithms for analysis of treatment effects in individual cases and small groups.

In the setting of causal assessment

In the setting of the causal assessment of the adverse events, for instance, in drug safety monitoring of an ongoing clinical trial or in post-marketing surveillance, the reports on the adverse events come one by one or by small groups. Typically, only the cases *with* adverse events are reported, and the cases with no adverse events are not. Thus, we rarely have an immediate opportunity of comparing cases with and without the adverse events. Also, while reports from a clinical trial contain relatively uniform information about patients, in spontaneous post-marketing surveillance reports, the description of one case can differ from the others with respect to the style of reported variables, their number, format, etc.; some can be numerical, some verbal, and so on, while some values may be missing.

Information on the incidence rates of the conditions (co-variates) potentially important for making a causal inference is likewise either insufficient, present in varied formats, is sourced from other populations, or lacking. Simply speaking, typically, the data are messy. Nevertheless, the inference as to whether this Adverse event, or Serious Adverse Event, for instance death, or a death threatening condition, is related or not related to the treatment, *must be made from this mess*. In many cases, based on this inference, *highly consequential decisions* must be made *immediately*, relying exclusively on the experience and intuition of a physician.

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In clinical medicine

The question of whether or not the treatment *A* was effective in patient *I* suffering from the disorder *D* is routinely asked and answered in everyday clinical practice. In the process of treatment, a physician must assess his or her strategy, assess if the selected treatment had a positive effect of the selected treatment, decide if an adverse event occurred and/or was or was not caused by the treatment, and make a decision to continue treatment, correct it, or discontinue it. This process, prediction of the effect in new cases and selection of the effective individualized treatment, is the foundation for accumulation of experience.

While the treatment decision should be made for each patient individually, the outcome of treatment in an individual patient does not necessarily confirm the result of the trial or observational data. Moreover, in many cases, systematic data on the effectiveness of this treatment in this disorder can be insufficient, controversial, unavailable, or absent.

In drug safety

We are interested in intended and unintended effect analysis as well as positive and negative treatment effects. To demonstrate the problem from an analytical point of view, we will use a model of causality assessment of adverse effects of treatment in an individual patient. In the area of drug safety, the methodology of causality assessment is most thoroughly developed and described, and the logic of analysis of the effect of treatment in individual and rare cases in clinical medicine – with all necessary reservations – is very similar to analysis of the causality of adverse effects.

The meaning of the term "causality" routinely used in pharmacotherapy, drug safety, and litigation does not entirely coincide with the meaning of this term in philosophy. In pharmacovigilance,[8] within causality assessment, an emphasis in the is placed on the connection between the exposure to a drug and the adverse event, and this aspect is designated as "relatedness." A possibility of exploring and interpreting other aspects of causality depends on the availability of information, the level of understanding of the mechanisms of the action of the drug, and the genesis of the adverse event. Our analysis will focus on this concept of "relatedness."

The use of any medical treatment can be accompanied with some adverse events, which can occur with or without relation to the treatment. The adverse reactions to the treatment, i.e., adverse events occurring because of treatment, pose substantial risks for individuals and a heavy social, economic, and financial burden for the general public's health and the entire society.[9] For these reasons, insofar as a serious adverse event occurs in a patient taking the medicine, all efforts have to be undertaken to determine causality of this event. If it is determined that the serious adverse event was caused by the medicine, necessary measures are to be taken, perhaps the treatment should be discontinued, or, depending on the severity of the adverse reaction and the magnitude of risk of its appearance in other patients, the medicine can be restricted in its use or completely taken off the market. Thus, the determination of causality of the treatment effects must be done as fast and as reliably as possible.

On the other hand, it is possible that the adverse effect can occur regardless of treatment. Misattributing a serious adverse effect to the treatment will also have a negative effect: patients will be denied a useful treatment, and the substantial resources expended for the development of this drug will have been spent in vain.

Importantly, the first inference about the causality of the adverse event rarely rests upon sufficient and systematically collected data, and this first inference is often extremely consequential. Most often,

[8]Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/ (Accessed 05/21/2017)
[9] Sultana, J, Cutroneo, P, and Trifirò G. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. 2013 Dec; 4(Suppl1): S73–S77.

this is done based on analysis of a single case or a few observed cases, that is, on the basis of limited and not necessarily systematically collected information, and in a limited timeframe. Another important factor is that the decision is typically made under severe emotional and social pressure. The person accountable for this decision should have a strong assurance as to the validity and reliability of the methods used for supporting this responsible decision.

Best practices

In every developed country, there is a system of laws and regulations aiming to warrant safety of drugs existing in and entering a market. Usually, a new medicine comes to a market only after its safety and efficacy have been thoroughly studied in clinical trials, and the use of this medicine has been approved by relevant regulatory agencies (Food and Drug Administration in the United States, European Medicines Agency in Europe, and other government agencies). As a result of this thorough and lengthy scrutiny, it is known and expected that although the new drug is generally safe, some kinds of adverse events can occur in patients taking it. This information is provided to patients, physicians, and pharmacists.

Usually, after a new medicine has entered a market, some reports surface about adverse events among the patients treated with this medicine, which have not been observed during the clinical trial. If these events, especially serious adverse events (SAEs), are found to be related to or possibly caused by, the medicine, there may be important clinical and economic implications. These include, but are not limited to, discontinuation of treatment for individual patients, including new warnings into informational documents provided to patients, physicians, and pharmacists, and ultimately a decision on keeping this medicine on the market or withdrawing it.

In the following brief description, we emphasize aspects of the process motivating the proposed algorithm, omitting other aspects of best practices necessary to drug safety professionals.

Typically, at the initial stages of the post-marketing experience, when a small number of patients have been exposed to the new treatment, the number of the reported events of interest cannot be large. The process starts as a single case or a few cases. This makes statistical analysis not feasible, but if the reported adverse event was serious (SAE), it is not possible to wait until number of analogous observations will become sufficient for making a statistically supported decision. A conclusion about the association of this adverse event to the medicine must be made as soon as possible, and the price of the right or wrong decision is measured in human lives lost and/or social and financial damage.

The importance of this problem has stimulated substantial efforts to developing an approach towards analysis of causality of adverse events in general, and particularly, in single and rare cases. [10]

The Food and Drug Administration (FDA) advises using the categories “probable,” “possible,” or “unlikely” for the categorization of causality. This classification addresses primarily the category of relatedness between the adverse event and drug (e.g., the adverse event A is *possibly* related to the drug D). The boundaries of the categories are not specified.

The World Health Organization (WHO) recommends the following categories:[11]

1. certain;
2. probably/likely;
3. possible;
4. unlikely;
5. conditional/unclassified; and
6. unassessable/unclassifiable.

[10] Jones JK, Causality assessment of suspected adverse drug reactions: A transatlantic view. Pharmacoepidemiology and Drug Safety. Volume 1, Issue 5, pages 251–260, September/October 1992

[11] World Health Organization, the Uppsala Monitoring Center, 2000, Safety Monitoring of Medicinal Products.

In assessing individual case reports, the FDA recommends[12] looking for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., Type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
2. Absence of symptoms related to the event prior to exposure;
3. Evidence of positive dechallenge or positive rechallenge;
4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established immunologic mechanisms of injury;
5. Consistency of the event with the known effects of other products in the class;
6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic safety studies; and
7. Absence of confounding (i.e., alternative explanations for the event, such as: there were no concomitant medications that could contribute to the event, there were no co- or pre-existing medical conditions).

With some minor differences, a similar approach is employed by the European Medicines Agency (EMA) and other agencies.

Thus, the approach toward the assessment of causality of adverse events in single and rare cases currently employed in clinical medicine and pharmacovigilance is essentially qualitative. In its most advanced form, the assessment procedure is semi-structured. This approach appears, given the complexity of analysis of single and rare cases, to be the best we can currently achieve, though we must acknowledge its limitations as an analytical and inferential framework. Given the complexity of the entire situation, the limited amount and a lack of uniformity of the data, and the high price of a wrong decision, it should be recognized that the regulatory agencies have structured the process in the best conceivable way, and they continue to perfect the guidelines for the causal assessment of the adverse events. Nevertheless,

1. The best practices process is complex and requires tremendous professional, time-oriented, and technical resources;
2. Assessment is qualitative, not quantitative; and
3. There is no model to counter the *hypothesis of relatedness* based on qualitative analysis.

The categories “related,” “possibly related,” “unrelated” are vague and subjective and therefore not supported by quantitative arguments.

Numerous attempts to formalize the process of causality assessment in single and rare cases have been undertaken.[13,14,15,16,17] The authors of these methods usually present them as instruments for analysis. In fact, these instruments, each in its own way, are good for standardizing and documenting the results of qualitative analysis of single cases. They prepare the cases for statistical analysis upon the accumulation of a sufficient number of observations, rather than providing a framework specifically for the analysis and for making causal inferences regarding individual and rare cases.

[12] Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.
[13] Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther. 1977 Mar; 21(3):247-54
[14] Naranjo C, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther, 30: 239-45, 1981
[15] Begaud B, Evreux JC, Joulard J and Lagier G (1985). Imputabilite des effets inattendus ou toxiques des medicaments; 40:111-8
[16] Venulet J, Ciucci AG, Berneker GC. Updating of a method for causality assessment of adverse drug reactions. Int J Clin. Pharmacol 1986; 24: 559-68
[17] Jones JK, Causality assessment of suspected adverse drug reactions: A transatlantic view. Pharmacoepidemiology and Drug Safety. Volume 1, Issue 5, pages 251–260, September/October 1992

Objectives

Our objective is to introduce

1. A computational approach to *causality assessment* for individual cases and small groups;
2. A framework stepping toward an algorithmic process of making inferences about *relatedness*; and
3. A set of rules and heuristics for best-effort statements about causality from incomplete information.

Notation

There is a terminological and methodological tradition for clinical trials and observational studies on the effects of treatment on morbidity and mortality. This paper focuses on binary outcomes, positive vs. negative, e.g., having a heart attack, or not having one, recovery or death. These are the most clear-cut clinical presentations of this dichotomy and the best way to present the concept. Continuous outcomes can be approached with similar principles, although more complex analysis should be required.

- An individual case I_i is described by a set of (binary) variables
  $I_i = (T_i, Y_i; A_i, B_i, C_i \ldots; \alpha_i, \beta_i \ldots)$; or alternatively $T(I_i) = T_i,\ A(I_i) = A_i$, etc.
- Treatment (T);
  - $T = 1$ is active treatment (also labelled T_+);
  - $T = 0$ is a lack of active treatment (also labelled T_-);
- Outcome (Y);
  - $Y = 0$ is the typical condition for the treated disorder (also labeled Y_-);
  - $Y = 1$ is a Serious Adverse Event (also labelled Y_+);
- Conditions (characteristics, properties);
  - A, B, C ...: include external and internal environments, and a time factor;
  - α, β ...: unknown or unobserved variables;
- Subjects come under the observation one by one or by small groups;
  - $I_1 = (1,0, A_1 \ldots, \alpha_1 \ldots)$;
  - $I_2 = (1,0, A_2 \ldots, \alpha_2 \ldots)$;
  - $I_3 = (1,1, A_3 \ldots, \alpha_3 \ldots)$; and
  - $I_4 = (0,1, A_4 \ldots, \alpha_4 \ldots)$.

Maximum achievable certainty

A causal assessment of severe adverse events can be executed under the circumstances that require making highly consequential decisions, in a short time, using limited and poorly systematized information. It does not allow time for collecting reliable data. It requires the utilization of all available sources and extracting reliable information from diverse, incomplete, and poorly systematized data to attain *maximum achievable certainty*.

In fact, the cited best practices for causal assessment follow this principle. Unfortunately, only the statement that the adverse effect of interest was not related to the treatment can be made in some cases, under obvious circumstances. Virtually in all other cases, the inference is expressed with amorphic term "possibly related," which is indeed maximum certainty achievable and acceptable under the level of responsibility and liability for the certainty, possibilities of qualitative analysis, as well as quality and quantity of available data.

We consider *maximum achievable certainty* as a principle guiding all the aspects of the causality assessment of the severe adverse events. Particularly, it is true regarding a structure of the clusters of conditions eventually associated with the treatment effect. Also, it is true for the estimates of the

probability of the outcome of interest: we are motivated to reach a level of *certainty maximum achievable* given currently available information.

In turn, achieving maximum possible certainty implies a possibility of utilizing all currently available information. Our algorithm is flexible regarding to the cardinality, structure, and content of the compared sets of data. It is substantially different from the instruments for causal assessment mentioned previously[13,14,15,16,17] which are based on an analysis of predefined sets of data. For various reasons, the authors of these instruments considered these predefined data to be most informative, which is not necessarily true for any analytical situation. Also, regardless of the content, the use of the predefined set of data makes the assessment of the cases impossible if at least some of the data were not reported. On the other hand, any reported data, which are not included in the predefined set and which eventually could be informative, are left out of consideration.

The computational aspects of the assessment require special treatment of the available data under this principle of *maximum achievable certainty*.

Computations on poorly systematized data

As mentioned previously, information on the incidence rates of the conditions (co-variates) potentially important for making a causal inference can be either insufficient or poorly systematized. They can present in varied formats, be obtained from various populations, or be outright lacking. They can be reported for a general population and/or its segments, for the defined population, or both. Even with the help of strong independence assumptions, we may not be able to attain population estimates of the marginal probabilities of the conditions.

To reduce uncertainty and subjectivity in quantification of poorly systematized data, we can form an upper bound on the population probability (incidence) of each condition as follows:

- If a population estimate is available, use it;
- If the condition is inherently rare relative to its complement (e.g., minor allele in genetic analysis), assume probability ≤ 0.5;
- If no other information is available, the probability is ≤ 1.

This kind of upper bound on a probability may be used to form a prior on the probability treated as a parameter.

The model

A patient is considered an individual and a member of a small group (2, 3, 4, …). The relationships between outcomes (Y) and treatment (T), known variables (V), and unknown variables α during a segment of time (t) are:

$$Y = f(T, V, \alpha, t).$$

In this paper, time will be presented as a sequence of incremental segments (cycles).

Our discussion refers to the model, in which all changes in treatment, as well as changes in outcomes occur discretely, incrementally by cycles:

$$t = t_1, t_2, \dots, t_i, t_{i+1}, \dots, t_n, \dots, t_t.$$

A cycle (t_i) is defined as a time segment long enough for treatment to exert its effect and for the outcome to be noted. Neither treatment nor outcome during one cycle is assumed dependent on another cycle. The events of treatment and outcome in a single individual during one cycle will be a unit of analysis. In specific studies, the duration of a cycle should be determined theoretically or empirically.

In their relationship to *t,* two major models will be considered. The first model – implicitly or explicitly – considers a single time period, which can be a single cycle or an aggregated segment of time comprised of several cycles.

The single period model is a component for another (longitudinal) model, in which time *t* is a sequence of adjacent segments (cycles) of time t_i . Each of the models will be described in two variants: 1) a single individual; and 2) a group of individuals. The first model (a single time segment), will be described in detail. The second model will be delineated in general.

Treatment

The term treatment (T), as it is understood in medicine and public health, is presented as a single value of binary variable ($T = 1$; not exposure to $Tx = 0$).

Outcome

The outcome of interest is interpreted as an intended or unintended change in the morbid condition of the individual ($Y = 1$), or a lack of change ($Y = 0$).

Treatment effect

We will use the definition of a causal effect of treatment by D. Rubin[18]: "Intuitively, the causal effect of one treatment, E, over another, C, for a particular unit and an interval of time from t_1 to t_2 is the difference between what would have happened at time t_2 if the unit had been exposed to E initiated at t_1 and what would have happened at t_2 if the unit had been exposed to C initiated at t_1: 'If an hour ago I had taken two aspirins instead of just a glass of water, my headache would now be gone,' or 'because an hour ago I took two aspirins instead of just a glass of water, my headache is now gone.' Our definition of the causal effect of the E versus C treatment will reflect this intuitive meaning."

Treatment-Outcome Complex

Regardless of the specific method, the assessment of the effects of treatment analyzes relationships between the exposure (vs. non-exposure) of a patient or patients to treatment and the outcome (positive and negative) among these patients, which create a 2×2 table (Table 1):

Table 1. Combinations of Treatment and Outcomes

	Tx_+	Tx_-
Y_+	Tx_+, Y_+	Tx_-, Y_+
Y_-	Tx_+, Y_-	Tx_-, Y_-

In our analysis, each patient is classified by the type of a treatment-outcome complex. There are four types of the treatment-outcome complex considering treatment and outcome not separately but rather as a unit.[19]

1. Patients exposed to Tx and having a positive outcome Y_+;
2. Patients exposed to Tx and having a negative outcome Y_-;
3. Patients not exposed to Tx and having a negative outcome Y_-; and
4. Patients not exposed to Tx and having a positive outcome Y_+.

Comparing the types of the treatment-outcome complex allows exploring the categories of "sensitivity to treatment" (St), and "capacity for spontaneous recovery" (Sp), which include the properties related to analysis of the treatment effect.

[18] Rubin, D. (1974). "Estimating Causal Effects of Treatments in Randomized and Nonrandomized Studies". J. Educ. Psychol. 66 (5): 688–701

[19] Sverdlov, L.S. 2011. Treatment-Outcome Complex and Analysis of Observational Data. In: Proceedings of the American Statistical Association, Section on Statistics in Epidemiology. Alexandria, VA, pp. 5415–5430.

Hereafter, by *property* we mean an attribute, quality, characteristic, ability or trait of a patient determined by a single factor inherent to a relevant category of patients (e.g., polymorphism), or by a confluence of multiple internal or external factors, either prevalent or rare.

Sensitivity to treatment

We interpret the category of sensitivity to treatment (the property "Sensitive") of an individual patient to a specified treatment as his or her ability and propensity to develop the outcome of interest in response to the treatment. The concept of sensitivity is relevant only in its relation to a specific treatment or treatments. We call a patient sensitive to a specified treatment St_{Tx} if this treatment has imposed the outcome of interest, whereas there are reasons to believe that it would not have occurred if a specified treatment was not applied.

Spontaneous emergence of outcome of interest

For most of the disorders listed in medical and public health classifications and manuals, spontaneous recovery, i.e., recovery (or remission, or intermission) without treatment, or regardless of treatment, is not a rare event. Spontaneous recovery in a substantial number of cases is well documented for a number of severe disorders, including smallpox, plague, cholera, anthrax, typhus, Ebola virus disease (EVD), myocardial infarction, cancer, asthma, pernicious anemia, disseminated sclerosis, rheumatoid arthritis, schizophrenia, depression, etc., and the list can be expanded indefinitely. The very necessity of the causal assessment of adverse events is due to the fact that they can be caused by treatment or emerge spontaneously, regardless of treatment. We interpret the capability for spontaneous emergence of the outcome of interest (the property "Spontaneous") as a predisposition of the individual for the emergence of the outcome of interest without treatment, or regardless of treatment. Hereafter, under this category, we mean an attribute, quality, characteristic, ability or trait of a patient determined by a single factor inherent to a relevant category of patients (e.g., polymorphism), or by a confluence of multiple internal or external factors, either prevalent or rare. Hereafter, the category "Spontaneous" will be designated as Sp_+, and a lack of this ability will be designated as Sp_-.

Assumptions: in statistical analysis

Some of the premises implicit in traditional statistical analysis, which we aim to bypass, are:

- Two or more events co-occur by chance unless the contrary is proven. Statistical models inherently involve randomness. The hypothesis of random co-occurrence of the events (null hypothesis) is accepted or rejected because of its correspondence (or a lack of correspondence) to the observed relationships.
- Subjects are anonymous and interchangeable. Personal information may move from one group to another for the reasons not related to analysis. Exclusion of any single subject from the study, moving him or her from one group to another, and/or trading single subjects between groups does not affect substantially the result of the study.
- Numerous subjects are required for making valid inferences.

Assumptions: in individual cases and small group analysis

In the causal assessment of adverse events in individual cases and small groups, we proceed from a different set of assumptions:

- Valid inferences potentially can be made from single and rare cases. This assumption is inherent to the very nature of the analysis. It must be emphasized that this is an assumption, not an assertion of fact.

- Each subject is a unique individual. Changing, removing, and/or adding individuals will completely change the subject and result of analysis.
- Two or more co-occurring events are related *unless the contrary is proven.* This assumption is the major motivating factor for analysis.

Logic: possibility and probability of relatedness

Our explorations are stemming from logic of Francis Bacon[20] who believed that the cause underlying a phenomenon should be deduced by elimination of the factors not matching the occurrence of the phenomenon, and inductive reasoning should be applied to the factors co-occurring with the phenomenon. For example, "…if an army is successful when commanded by Essex, and not successful when not commanded by Essex: and when it is more or less successful according to the degree of involvement of Essex as its commander, then it is scientifically reasonable to say that being commanded by Essex is causally related to the army's success."[21]

Importantly, Bacon emphasized that this inference is not a final conclusion. Rather it is only a hypothesis, which must be scrutinized and compared to other hypotheses.

Inferences from "treatment-outcome complex"

Our search starts with logical analysis of the types of the "treatment–outcome complex," which provides limited but still substantial opportunity for causal inferences. Proceeding by enumeration of possible cases:

- If Tx_+, Y_+ was observed, the outcome Y_+ could be caused by the treatment Tx_+; also, it could occur regardless of Tx_+
- If Tx_-, Y_- was observed, a direct conclusion regarding the effectiveness of treatment Tx_+ cannot be made
- Tx_+, Y_- was observed, it can be said with certainty that Y_+ was not the effective treatment for the patient, which is logically equivalent to the statement that the patient was not sensitive to Tx_+; and
- Tx_-, Y_+ was observed, it is possible to state, also with certainty, that Y_+ was not caused by Tx_-, i.e., the outcome Y_+ has occurred spontaneously.

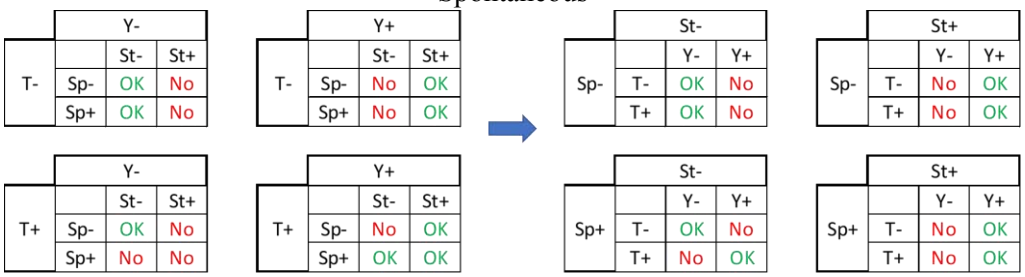
Then, it can be inferred, in symbols:

$$T_+, Y_+ \rightarrow St_+ \text{ or } Sp_+;$$
$$T_+, Y_- \rightarrow St_- \text{ and } Sp_-;$$
$$T_-, Y_+ \rightarrow St_+;$$
$$T_-, Y_- \rightarrow St_-;$$

In particular, this logic is shown as the following schematic (Table 2). The left side of the table indicates a presence of the categories of "Spontaneous" and "Sensitive" in all possible variants of the "treatment-outcome complex." The right side of the table demonstrates the outcome prospectively expected in individuals having all possible combinations of the categories "Spontaneous" and "Sensitive."

[20] Francis Bacon. New Organon, English translation, based on the 1863 translation of James Spedding, Robert Leslie Ellis, and Douglas Denon Heath. http://www.constitution.org/bacon/nov_org.htm (Accessed 9/22/2018).
[21] Hesse, M. B. (1964), "Francis Bacon's Philosophy of Science", in A Critical History of Western Philosophy, ed. D. J. O'Connor, New York, pp. 141—52

Table 2. Relationships between the Categories of Treatment-Outcome Complex, Sensitivity and Spontaneous



Pairwise comparisons

Information about the "treatment-outcome complex" enables mapping the properties (conditions) under the categories "Spontaneous" and "Sensitive." It can be achieved by comparing two (or more) individuals. As a reminder, the result depends on a quantity and quality of available information, and all logical operations are made under the strong assumption that two or more co-occurring events are related *unless the contrary is proven.*

Let us consider the following set of individuals:

$$I_1 = (1,0, A_1 \dots, \alpha_1 \dots)$$
$$I_2 = (0,0, A_2 \dots, \alpha_2 \dots)$$
$$I_3 = (1,0, A_3 \dots, \alpha_3 \dots)$$
$$I_4 = (0,1, A_4 \dots, \alpha_4 \dots)$$
$$I_5 = (1,0, A_5 \dots, \alpha_5 \dots)$$
$$I_6 = (0,0, A_6 \dots, \alpha_6 \dots)$$
$$I_7 = (1,0, A_7 \dots, \alpha_7 \dots)$$
$$I_8 = (0,1, A_8 \dots, \alpha_8 \dots)$$
$$\dots$$

While the "treatment-outcome complexes" in individuals $I_{1,\dots 4}$ are identical to the respective individuals $I_{5,\dots 8}$, some of the properties (conditions) in each unique individual may coincide with that property in its counterpart, and the others may be different. In a small group of observations, we can compare them pairwise, explore similarity and dissimilarities in their descriptions, and link them to the treatment-outcome complex.

Table 3. Pairwise Comparisons

		I1	I2	I3	I4
		T+ Y+	T- Y-	T+ Y-	T- Y+
I1	T+ Y+	N/A	C1	C2	C3
I2	T- Y-	C1	N/A	C4	C5
I3	T+ Y-	C2	C4	N/A	C6
I4	T- Y+	C3	C5	C6	N/A
I5	T+ Y+	C7	C1	C2	C3
I6	T- Y-	C1	C8	C4	C5
I7	T+ Y-	C2	C4	C9	C6
I8	T- Y+	C3	C5	C6	C10

Table 3 shows all 32 possible types of comparisons (C_i) by the treatment-outcome complex. Ten unique types of comparisons are highlighted, and the remaining are types are redundant.

Unique types of comparisons highlighted in Table 1 are shown separately in Table 3, demonstrating similarity-dissimilarity of the compared treatment-outcome complexes, which in turn

enable mapping the properties associated with the categories "Spontaneous" and "Sensitive" among the sets of the variables describing the individuals.

Table 4. Unique Types of Pairwise Comparisons

C1	T- Y-	vs.	T+ Y+
C2	T+ Y-	vs.	T+ Y+
C3	T- Y+	vs.	T+ Y+
C4	T+ Y-	vs.	T- Y-
C5	T- Y+	vs.	T- Y-
C6	T- Y+	vs.	T+ Y-
C7	T+ Y+	vs.	T+ Y+
C8	T- Y-	vs.	T- Y-
C9	T+ Y-	vs.	T+ Y-
C10	T- Y+	vs.	T- Y+

Small group: mapping conditions and constructing hypothesis

The scenario described here emulates typical events in the drug safety setting. A small group of individuals, I_1, I_2, I_3, I_4 (Table 5a), come under observation one by one in this order. Accordingly, this group will be analyzed stepwise (4b,c,d). Each of the members of this group has been described with a set of variables *T,Y,A,B,C,…X,Z*. All speculations in this section are being made under the assumption *Two or more co-occurring events are related unless the contrary is proven*.

Table 5. Mapping Conditions

Table5a. Observed individuals

	T	**Y**		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	U	V	W	X	Z		α
I1	1	0		0	0	0	0	1	0	1	0	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	1		α1
I2	1	0		0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	0	0	0	1	0	0	0	1	0		α2
I3	1	1		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3
I4	0	0		1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	1		α4

Table 5b. Distinct (designate as I3-I1):

	T	**Y**		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	U	V	W	X	Z		α
I1		0			0			1		1	0			1		0	0	1	1		1			0			1		α1
I3		1			1			0		0	1			0		1	1	0	0		0			1			0		α3

Table 5c. Sequential elimination of potential causes:

	T	**Y**		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	U	V	W	X	Z		α
I1	1	0		0	0	0	0	1	0	1	0	1	1	1	0	0	0	1	1	0	1	1	0	0	0	1	1		α1
I2	1	0		0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	0	0	0	1	0	0	0	1	0		α2
I3	1	1		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3
I4	0	0		1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	1		α4

Sp	St
Sp-	St-
Sp-	St-
Sp+ OR St+	
Sp- OR Sp+	St-

Table5d. Conditions potentially associated with Sp and St:

I3-I1				1			0		0	1			0		1	1	0	0		0			1			0		
I3-I1-I2				1					0						1								1					
I3-I1-I2-I4				1											1													

May be associated with
St, Sp, or both
St, Sp, or both
St only

From their treatment-outcome complexes we can infer that the individuals I_1 and I_2 came under observation for a reason not related to the event of interest, e.g., a reported adverse event unrelated to Y. Because the treatment-outcome complex of the cases I_1 and I_2 is T_+, Y_-, neither of the elements of their description can be associated with the categories "Sensitive" (St), or "Spontaneous" (Sp). The individuals I_1 and I_2 are baseline members of the group, and their descriptions will be compared with other members.

Possibility of relatedness

Individual I_3 was exposed to the same treatment (T_+) and exhibits the serious adverse event Y_+. The descriptions of I_3 and I_1 contain a subset of variables which is identical in both individuals, as well as a subset of variables differing from one individual to the other (Table 4b). We infer that the variables found in I_3 with identical values in I_1 cannot be related to both (T_+, St, and Sp). To the contrary, the variables distinct from I_1 *may* be related to T_+, St, and/or Sp. Quantitative characteristics of this possibility will be considered later in this paper.

Comparing I_3 with I_2 does not change the composition of the subset of variables related to T_+, St, and/or Sp. This subset can be narrowed down after comparing I_3 with I_4. The latter has the treatment-outcome complex T_-, Y_-, which means that the variables describing I_4 cannot be associated with Sp. Therefore, variables identical in I_3 and I_4 must be eliminated from the list of those potentially related to T_+, St, and/or Sp.

Constructing hypotheses via sets of conditions

Now, we can formulate hypotheses about clusters of conditions that *may* be causally related to the outcome Y_+ (the adverse event). We proceed by constructing pathways; that is, we begin with a baseline group member, and sequentially compare that individual with one or more other individuals, eliminating variables as we go.

At the first step (pathway $I_3 - I_1$), the hypothesis is that the outcome Y_+ *may* be related to the cluster of conditions $B_+, E_-, G_-, H_+, K_-, M_+, N_+, O_-, P_-, R_-, V_+, Z_-$, which can represent either the category "Sensitive," or "Spontaneous," or both. The potential causes can be sequentially eliminated (Table 4c) via pairwise comparison of the individuals coming under observation, i.e., the hypothesis can be narrowed.

At the second step (pathway $I_3 - I_1 - I_2$), the cluster of the potential candidates for relatedness to the outcome Y_+ is reduced to B_+, G_-, M_+, V_+. This cluster still can represent either St, or Sp, or both.

At the third step, (pathway $I_3 - I_1 - I_2 - I_4$), the cluster is reduced to B_+, M_+, which may represent only the category St. Therefore, we have formulated the hypothesis about the cluster of conditions to B_+, M_+ *may* be causally related to the outcome Y_+ (in our case, a serious adverse event).

In this context, the addition of new cases, or increasing the set of available descriptors and corresponding population estimates, can further increase or decrease the cluster. At the extreme, all possible causes from the set of known variables will be eliminated, leaving the possibility of mapping the factors St or Sp, or both, to the subset α_i of unknown variables. In this sense, the hypothesis is as good as the available information, and with sufficient information, this approach can be generalized to the analysis of the heterogeneity of the treatment response.

The hypothesis above integrates three major components: treatment, outcome, and "generating conditions." It is deduced from a series of eliminations and inclusions of the conditions, based on the assumption that *two or more co-occurring events are related unless the contrary is proven*, i.e., essentially, the generated hypothesis is deterministic. The existence of the subset of unknown or unobserved variables α_i implies that under any circumstances some share of uncertainty remains despite the apparent determinism.

Alternative hypothesis

The alternative to the deterministic hypothesis above is the hypothesis of random association between the designated clusters of conditions and the outcome. Examining this hypothesis requires computing the probability of observing individuals with these conditions in the population. The simplest model, assuming independence, for the cluster of variables associated with pathway $I_3 - I_1 - I_2$ would be:

$$\Pr(B_+, G_-, M_+, V_+) = \Pr B_+ \times \Pr G_- \times \Pr M_+ \times \Pr V_+ ;$$

For pathway $I_3 - I_1 - I_2 - I_4$, it would be:

$$\Pr(B_+,\ M_+) = \Pr B_+ \times \Pr M_+.$$

We do not necessarily have population incidence estimates for each variable, but we can constraint some probabilities by 0.5 as the more rare of the two possibilities, and treat other probabilities as unknown and unconstrained, as in this example:

$$\Pr(B_+) \le (\Pr B_-) \to \Pr(B_+) \le 0.5;$$
$$\Pr(G_+) \le (\Pr G_-) \to \Pr(G_-) \le 1;$$
$$\Pr(M_+) = 0.3;$$
$$\Pr(V_+) = 0.7;$$
$$\dots$$

Then:

$$\Pr(B_+, G_-, M_+, V_+) = \Pr B_+ \times \Pr G_- \times \Pr M_+ \times \Pr V_+ \le 0.5 \times 1 \times 0.3 \times 0.7 \le 0.105;$$
$$\Pr(B_+,\ M_+) = \Pr B_+ \times \Pr M_+ \le 0.5 \times 0.3 \le 0.15.$$

Modeling the conditional probability of the Adverse Event

We are interested in the probability of the Adverse Event Y_+ among individuals with the complex of conditions we have identified as a hypothesis, i.e. $\Pr(Y_+|B_+, G_-, M_+, V_+)$. Within our sample, all such individuals are T_+, so a direct empirical frequency estimate is not feasible.

However, we can estimate the conditional probabilities given individual conditions, $\Pr(Y_+|B_+)$, $\Pr(Y_+|G_-)$, etc. The simplest model for combining these probabilities is the Naïve Bayes approach as follows:

$$\frac{\Pr(Y_+|B_+, G_-, M_+, V_+)}{\Pr(Y_-|B_+, G_-, M_+, V_+)} = \frac{\Pr(Y_+|B_+)}{\Pr(Y_-|B_+)} \frac{\Pr(Y_+|G_-)}{\Pr(Y_-|G_-)} \frac{\Pr(Y_+|M_+)}{\Pr(Y_-|M_+)} \frac{\Pr(Y_+|V_+)}{\Pr(Y_-|V_+)}$$

Suppose the following population estimates and constraints:

$$\Pr(Y_+|B_+) = 0.6$$
$$\Pr(Y_+|G_+) = 0.7$$
$$\Pr(Y_+|M_+) = 0.7$$
$$Y_+|V_+ - \text{rare event} \to \Pr(Y_+|V_+) \le 0.5$$

Given these estimates and the variable selection information implied by pathway $I_3 - I_1 - I_2$:

$$\frac{\Pr(Y_+|B_+, G_-, M_+, V_+)}{1 - \Pr(Y_+|B_+, G_-, M_+, V_+)} \le \frac{0.6}{0.4} \times \frac{0.7}{0.3} \times \frac{0.7}{0.3} \times \frac{0.5}{0.5} = 14$$
$$\Pr(Y_+|B_+, G_-, M_+, V_+) \le \frac{1}{1 + \frac{1}{14}} = 93.3\%$$

Thus, the probability (incidence) of an individual with the cluster B_+, G_-, M_+, V_+ in the defined population is 10.5%. The probability of the outcome Y_+ among individuals with the complex of conditions B_+, G_-, M_+, V_+ is bounded by 93%, but it is not known to what extent it could be attributed to sensitivity to the treatment and/or to spontaneous occurrence of the outcome Y_+.

Addition of information about individual I_4 (pathway $I_3 - I_1 - I_2 - I_4$) enables the estimation of the contribution of sensitivity to the treatment to the development of the outcome Y_+.

$$\frac{\Pr(Y_+|B_+, M_+)}{\Pr(Y_-|B_+, M_+)} = \frac{\Pr(Y_+|B_+)}{\Pr(Y_-|B_+)} \frac{\Pr(Y_+|M_+)}{\Pr(Y_-|M_+)}$$

$$\frac{\Pr(Y_+|B_+,M_+)}{1-\Pr(Y_+|B_+,M_+)}=\frac{0.6}{0.4}\times\frac{0.7}{0.3}=3.5$$

$$\Pr(Y_+|B_+,M_+)=\frac{1}{1+\frac{1}{3.5}}=77.8\%$$

This means that with the incidence of the cluster B_+, M_+ in the defined population is 15%, and the probability of the adverse event of interest (Y_+) among individuals with this cluster is 77.8%. In this case it can be attributed to the property St.

A further increase in the number of observations, particularly individuals with the treatment-outcome complex Tx_{-}, Y_+, in the sample, will make the estimate more precise. Also, the increase of the sample can lead to another improvement via obtaining the estimates of the probability of the Y_+ conditional on the modality of treatment.

Single case and longitudinal models

In clinical medicine, pharmacovigilance, and in other areas, there may be circumstances requiring a responsible decision to be made for an individual case without any information about other individuals. One way or another, the existing approaches towards analysis of single cases[1,2,3,4,5,6] use longitudinal models. The available literature does not appear to contain methods that would fit the practical needs for causal assessment in individual cases in the areas listed above.

One of the instruments used for causal assessment in individual cases in many areas is the protocol "challenge, de-challenge, re-challenge" (CDR). In the frame of the CDR protocol, the emergence of the adverse event after the initiation of treatment, its disappearance after discontinuation of treatment, and reappearance after resuming the treatment is an intuitive argument in favor of the association between the treatment and the adverse event, but this intuition can rarely be supported with quantitative arguments.

Usually, in an individual patient, only one or two segments of the CDR protocol can be observed. All relevant components rarely appear together twice, and almost more than twice. Inferences can be problematic due to the small number of observed co-occurrences, due to the need to interpret the CDR protocol outside the context of conditions under which this protocol was taking place, as well as the diversity of temporal patterns of treatment and adverse effects.

A possibility of a causal assessment in quantitative terms can be improved substantially if temporal characteristics of the treatment process are available, specifically if the duration of the cycle and the incidence rate of the adverse event are known.

Table 6. Individual Treatment Process

6a

	T	**Y**		*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*R*	*S*	*U*	*V*	*W*	*X*	*Z*		α
t1	0	0																											α3,1
t2	0	0																											α3,2
t3	0	0																											α3,3
t4	1	1																											α3,4
t5	0	0																											α3,5

6b

t1	0	0		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3,1
t2	0	0		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3,2
t3	0	0		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3,3
t4	1	1		0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	0	1	0	1	0	1	0	1	0		α3,4
t5	0	0		0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	0	1	0		α3,5

Let individual I_3 be observed during uneventful cycles t_1, t_2, t_3 (Table 6). At the cycle t_4, she was exposed to treatment T_+ and presented with adverse event Y_+. At cycle t_5, the treatment T_+ was discontinued and the adverse event Y_+ subsided (Table 6a). This simplistic model lacks numerous details substantial from both analytical and a drug safety perspective (e.g., grace period, relapse, etc.). Still, this description of the CDR protocol makes possible mathematical modeling, starting from a most general model:

$$\Pr(Y_{t_i}|T_i) = f(C_{t_i})$$

The probability depends on the set of conditions, which vary over time, but not explicitly on time itself (the stationarity assumption). In principle, we can then compute the probability of random co-occurrence of the treatment T_+ and adverse event Y_+ during the cycle t_4 given other characteristics. This makes possible applying the principles of analysis of a small group described previously.

Summary

The proposed heuristics is an exploratory procedure. It starts with a set of essentially deterministic assumptions, including: *1) Valid inferences potentially can be made from single and rare cases; 2) Each subject is a unique individual; and 3) Two or more co-occurring events are related unless the contrary is proven.* It proceeds with a logical analysis of the available single observation or few observations, at least one of which has the outcome of interest. The observations are compared by the treatment-outcome complex and conditions. The factors not matching with the outcome of interest are interpreted as *not* involved in the development of the outcome of interest, and are therefore eliminated.

The remaining known factors, as well as unknown or unobserved factors, *may* have a causative role. The factors potentially having a causative role are classified under the categories of sensitivity to treatment (St) and a capacity of spontaneous occurrence of the outcome of interest (Sp), both, or neither. Thus, a hypothesis has been formed suggesting the relatedness between the treatment and the outcome of interest, intermediated by a cluster of conditions potentially representing a property of sensitivity to the treatment.

This part of our explorations follows the logic of Francis Bacon, who believed that a hypothesis based on observations is, per Francis Bacon, just a "First Vintage," not a final conclusion. The hypothesis must be scrutinized and compared to other hypotheses, or per Karl Popper, be “falsified.”

In the second part of the heuristics, the initial deterministic hypothesis is contrasted with the hypothesis of random co-occurrence of the outcome of interest with the factors, which were hypothesized to be potentially causative. This is a probabilistic, statistical hypothesis based on the following assumptions: 1) *Two or more events co-occur by chance unless the contrary is proven; and* 2) *Subjects are anonymous and interchangeable.*

Since we are dealing with single cases and small groups, we cannot, as in traditional statistical analysis, take advantage of the law of large numbers, requiring numerous subjects in order to make valid inferences. This requirement can be loosened, taking advantage of modern statistical and computational approaches. Particularly, a probability of the outcome of interest conditional on the probability of the factors implicated for a potential causal role can be estimated using population estimates of the factors and a Bayesian stochastic model, which allows for an appropriately limited inference given limited data. Although these approaches leave unanswered theoretical questions regarding the underlying assumptions[22], the validity of the results is confirmed by numerous practical applications.

[22] Lamont A, Lyons M, D, Jaki T, Stuart E, Feaster DJ, Tharmaratnam K, Oberski D, Ishwaran H, Wilson DK, Van Horn, ML. Identification of predicted individual treatment effects in randomized clinical trials. https://doi.org/10.1177/0962280215623981 (Accessed 12/20.2017)

Thus, the algorithm for the causal assessment in individual cases and small groups, the principles of which are described in our heuristics, includes:

- Contrasting the deterministic and probabilistic hypotheses of co-occurrence of the treatment and the AE;
- Analyzing three major components: treatment, outcome, and conditions (including internal, external environment, and time factor);
- Using a principle of a *maximum achievable certainty* in addressing the problem of non-systematically collected data; and
- Operating with the concepts "treatment-outcome complex," "sensitivity to treatment (St)," "spontaneous occurrence of the AE (Sp)," which might allow for:
    - Identifying clusters of conditions potentially associated with (1) sensitivity to treatment and (2) capacity for the spontaneous occurrence of the outcome of interest, and determine the incidence of patents with such clusters in the defined population; and
    - Providing quantitative estimates of the probability (incidence) of patients with the clusters of factors potentially associated with the properties of sensitivity to treatment and spontaneous occurrence of the AE in question.

In the described heuristics, sensitivity to treatment (St) is identified as an indicator of the relatedness between the treatment and AE. The relatedness between the treatment, AE, and conditions, is assessed via two estimated probabilities: the probability of the occurrence of the AE under the conditions representing St, and (2) the probability of the AE in question conditional on the clusters of factors potentially associated with sensitivity to treatment is provided. The proposed algorithm compensates for the insufficient number of observations by making use of comprehensive description of the cases, Bayesian inference, and stochastic modeling of the relationships among treatment, AE, and conditions.