AT THE ORIGIN OF COMPLIANCE
DISCRETE CHOICE EXPERIMENT TO ELICIT THE PREFERENCES OF PATIENTS, CLINICIANS AND PAYORS

This statistical method was developed in the '70s as a marketing tool to investigate the market factors and characteristics that orient consumer choices. From the 2000s, it made its debut also in the biomedical field and it is used with increasing interest, for example to identify the ideal treatment in a given setting.

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It is only a short step from marketing to the biomedical sector. In effect, knowing how much we are prepared to pay to purchase a consumer good with certain characteristics and advantages is not so different from knowing how much we are willing to accept in terms of side effects in exchange for a therapy that can have a significant impact on a disease. This, in short, is the principle underlying the Discrete choice experiment (Dce), a method based on conjoint analysis, which enables us to evaluate in quantitatively and statistically solid terms the preferences of patients, doctors or payors vis-à-vis different therapeutic options or possible scenarios in the management of chronic pathologies or pharmacoeconomic analyses.

The method was actually developed at the beginning of the 70s from the studies of psychologists, mathematicians, econometricians and market analysts, with the aim of understanding what factors orient people's choices and lead them to prefer one product over another. Only in more recent times – and above all after the Nobel prize for economics was won by Daniel Little McFadden in 2000 for his contribution to the development of theory and methods – has Dce become widespread also in the pharmaceutical and healthcare field in general. Since then, interest in this method has grown considerably, both in the academic and private sector and in particular in the biomedical field, where the studies carried out with Dce and published in recent years in scientific journals have grown almost exponentially. Also in Italy, interest in use of the method is beginning to grow in various therapeutic areas.

HOW DCE WORKS

The objective of Discrete choice experiment is to determine the drivers of choice in different target populations, which can be patients, but also clinicians, payors and any other stakeholders who have a role in the clinical decision-making processes. So much so that, in the works published at international level, an increasing number of studies directly compare several target populations on the same theme. In particular, DCEs that evaluate the approaches of doctors and patients, highlighting the differences between the respective preferences and therefore guiding related decisions, are widely used. To carry out a Dce survey, we start from the definition of a series of variables, i.e. characteristics of the product or the provision in question (known as attributes) and their levels that represent the ways in which the attributes are manifested.

"For example, in the case of an evaluation of different treatments available for a disease, the target can be the patient who is faced with various therapeutic options" explains Patrizio Pasqualetti, lecturer in medical statistics at Università La Sapienza in Rome, and author of several scientific works conducted with Dce. "Each patient will respond to different stimuli (choice task) relative to the possible treatments, which are broken

down into their main components (Dce is also called breakdown method because a concept, in this case a treatment, is broken down into its components). Healthcare treatments in general can be broken down into three broad categories: effectiveness, side effects and method of administration. Costs can be added as another category, a variable widely used abroad but not in Italy, since the patient receives the treatment free of charge via the national health system".

Each of these attributes in turn presents with different levels. For example, the "risk of nausea as a side effect" attribute could present with three levels, i.e. with a frequency of 5%, 10%, 20%. The attributes and levels are established at the beginning of the study based on the literature data (in general taken from the clinical trials) or referring to clinical experience. Lastly, the attributes and levels selected are combined to form a series of "treatments", representative of all the possible combinations. These are then entered in a questionnaire and presented as a sequence of comparisons between pairs of "treatments" from which the respondent has to choose the one preferred. Currently DCEs can be performed with the support of IT platforms that manage the entire process of targets' inclusion and remote collection of the responses.

THE CASE OF DIABETIC TREATMENT

In an example cited by Pasqualetti, Dce was used in the field of diabetes to investigate patient preferences concerning different classes of drugs currently available to obtain satisfactory metabolic control of type 2 diabetes.

The characteristics of the treatment (or attributes) entered in the questionnaire administered to the patient included the capacity to reduce

glycemia (effectiveness); the timing of administration, in terms of dose and frequency of use (method of administration); stomach problems and hypoglycemia (side effects). Weight loss (secondary effectiveness), possible increase in the risk of heart failure and the cost of the therapy were also taken into consideration. "In this case treatments A and B were the same in terms of effectiveness, because they resulted in the same reduction in glycemia, and the probabilities of suffering stomach problems and weight loss were also the same" explains Pasqualetti. "However, treatment A had the advantage of a simpler method of administration,

because it required two instead of three tablets a day and also entailed a lower risk of heart failure. Treatment B was preferable because it was associated with a lower number of hypoglycemia episodes and it cost less. The patient, who is obliged to choose between these two treatments, necessarily has to give up something and by indicating his/her preference implicitly shows to which product characteristics he/she has given greater importance".

HOW MUCH PATIENTS ARE WILLING TO "PAY"?

In addition to the end user preferences, the questionnaire also gathers other information such as age, gender, education etc., allowing a more sophisticated analysis useful for better interpreting the responses and segmenting the respondents based on significant criteria (for example the preferences of a young patient can be different from those of an elderly person, those of a first-time patient may be different from those of a relapsed patient, and so on). In this way, thanks to the overall analysis, it will be possible to identify and quantify the attribute and the level that has the greatest "weight" in terms of preferences and which the respondents are not willing to give up. It is also possible to prioritize the right attributes

Example of questions put to patients in the diabetes area

Medicine feature	Medicine A	Medicine B
Decrease in average blood sugar level	120 130 140 150 160 170 180 190 200 210 220 mg/dl Controlled · Need some more control · Need a lot more control	120 130 140 150 160 170 180 190 200 210 220 mg/dl Controlled · Need some more control · Need a lot more control
Daily dosing schedule	Morning · Evening	Morning · Evening
Chance of stomach problems	23 out of 100 (23%)	23 out of 100 (23%)
Frequency of low blood– sugar episodes	1 – 2 per month (12 – 24 per year)	1 – 2 per year
Weight change	No weight change	No weight change
Increased chance of CHF	0 additional people out of 100	3 additional people out of 100
Personal medicine cost	$200 per month	$100 per month
Which medicine would you choose i these were the inly two medicines available?	Medicine A	Medicine B

How likely would you be to miss or skip doses of each medicine?	Much more likely to miss or skip doses with Medicine A	A little more likely to miss or skip doses with Medicine A	Equally likely to miss or skip doses with Medicine A and Medicine B	A little more likely to miss or skip doses with Medicine B	Much more likely to miss or skip doses with Medicine A

(with their levels) and infer the algorithm of choice for the doctors, patients, payors etc. In this way, thanks to the overall analysis, it will be possible to identify and quantify the attribute and the level that has the greatest "weight" in terms of preferences and which the respondents are not willing to give up. It is also possible to prioritize the right at-tributes (with their levels) and infer the algorithm of choice for the doctors, patients, payors etc.

In another work cited by Pasqualetti, for example, it emerged that among the variables of different therapeutic treatments compared, the side effects were considered more important than the effective-ness, followed by the method of administration. "Dce tells us what the most important characteristics are for a patient and details the side effects that are most difficult to accept" he continues. "It also enables us to quantify to what extent a patient is willing to accept a side effect on condition that the treatment results in an increased life expectancy. This is a very important aspect in oncology, for example".

PROMOTING COMPLIANCE

As is known, clinician and patient preferences, in terms of therapies prescribed and followed, do not always coincide and this method helps the clinician to identify the "best" therapy for the patient. The doctor could decide to prescribe a medicine taking account of the preferences expressed by the patients based on analysis of the results of a Dce study involving both populations. And this, as demonstrated by extensive scientific literature, has a positive and significant impact on compliance, which rep-resents a common objective for the doctor, the patient and the government (the payor). "If the patient receives the treatment chosen by himself/herself, there is a greater probability that he/she will adhere to the therapy" confirms Pasqualetti. This has also emerged from some works in which the questionnaires included questions in this regard, in which the respondents stated that they would probably have skipped several doses of the non-chosen treatment. Compliance is high in the clinical trials because the patients are followed up, but in real life compliance tends to de-crease or to be insufficient for obtaining the clinical benefits of the therapies.

Including the patient by allowing him/her to express a preference on the treatment to be followed could have an important outcome in terms of compliance.

"Also according to the Consort (Consolidated Standards of Re-porting Trials) declaration drawn up by a group of scientists, clinicians and editors to improve the quality of randomized clinical study re-ports, it is underlined, with regard to generalizability of the results (ex-ternal validity), that patient preferences should be given due consideration and integrated in the so-called therapeutic alliance, which could favor an improved relation-ship, compliance with and aware-ness of the treatments adminis-tered" adds Pasqualetti.

THE APPLICATIONS (INCLUDING COVID-19)

Dce has recently been used in many different applications and therapeutic areas. The field of in-ternal medicine/general medicine has the highest number of studies (233), followed by

pharmacy and pharmacology (132) and oncology (109). However, the applications would not be complete without Covid-19, an area in which the method is used to evaluate the trade-off (understood as the cost/benefit ratio) between containment measures and spread of the epidemic. For example, evaluating the point of equilibrium be-tween reduction of the risk of being infected or infecting others and the economic losses associated with the lock-down and its duration. Other applications concern building consent on clinical or scietific problems or problems relating to the treatment pathway, using a more solid and scientific tool than other widely used methods (like Delphi). Or defining together (clinicians and patients) new modes of access and management of chronic diseases at local level following the problems caused by the Covid pandemic. Drawing up new Quality of Life models for the patient. Lastly, developing psychometric scales and indexes for objectively and comparably evaluating/measuring certain parameters (for example building a psychometric scale for evaluating the effectiveness of treatments for head-ache).

THE "IDEAL" DRUG

The idea is not only to compare existing treatments, but also to "create" new ones – at least on paper – that have the characteristics desired by the end users or the prescribing doctors and that can also guide the choices of the pharmaceutical companies. Pasqualetti tells us that when a Dce is constructed, due to the numerous combinations created (to identify a product or a ser-vice defined with four attributes, each of which has three levels, we would have 81 different hypothetical "scenarios" or "treatments"), products can be composed that do not exist in reality, but are potentially interesting for the patients and the clinicians. "When the company understands what the important at-tributes are, it can steer in that di-rection to develop a drug, because it already knows that the patient or the clinician will prefer it" comments the professor. "Dce is one of the many cost/benefit analyses, but it also allows us to find ideal combinations. Or it can bring out the fact that important characteristics for the clinicians are actually not relevant for the patients".

CLINICIANS AND PAYORS

In addition to the patients, the end users of the analysis can also be the clinicians, in order to elicit their preferences in terms of products to be prescribed, and payors or bodies like the regulatory agencies who have to decide the refundability of a treatment. For example, in the case of an innovative cancer drug with very high cost, it is important to know the drivers that guide the choices of the clinician and the patient, but also those of the payors who have to establish the trade-off between the value and the improvement offered by the new drug and the cost of introducing the innovation and evaluating its economic sustainability. In 2004 an editorial published in the Bmj (Discrete choice experiments in health care) – one of the first works to discuss Dce in the biomedical field – suggested that the method should be used also by the National Institute for Health and Care Excellence (Nice). "Aifa [the Italian drug agency] could give importance to patient preferences – concludes Pasqualetti – and likewise a company or a hospital, which can decide to opt for one treatment or another". However, it is wrong to think that Dce is opposed or alternative to other tools currently used to investigate patient choices, like patient-reported outcomes (Pro). The same editorial in the Bmj suggested integrating it with the tools already available, as a further method for including the patient and understanding his/her preferences.

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