RESEARCH ETHICS

Quantitative aspects of informed consent: considering the dose response curve when estimating quantity of information

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Information is usually supposed to be a prerequisite for people making decisions on whether or not to participate in a clinical trial. Previously conducted studies and research ethics scandals indicate that participants have sometimes lacked important pieces of information. Over the past few decades the quantity of information believed to be adequate has increased significantly, and in some instances a new maxim seems to be in place: the more information, the better the ethics in terms of respecting a participant's autonomy. The authors hypothesise that the dose-response curve from pharmacology or toxicology serves as a model to illustrate that a large amount of written information does not equal optimality. Using the curve as a pedagogical analogy when teaching ethics to students in clinical sciences, and also in engaging in dialogue with research institutions, may promote reflection on how to adjust information in relation to the preferences of individual participants, thereby transgressing the maxim that more information means better ethics.

Today, informed consent is a key issue when recruiting participants in clinical research, and is in line with the ideal of good clinical practice. This applies, at the very least, in North America and Western Europe. The consent requirement serves the important function of safeguarding the individual from harmful interventions and information is seen as a prerequisite for rational decisions concerning participation in clinical research. According to the Helsinki Declaration, adequate information must be comprehensible and meet the following demands: the information should be given both orally and in writing, and potential participants are to be informed generally about the purpose and design of the study, what it means to participate, the pro and cons of the study, voluntariness with regard to participation, and the option to withdraw.

Previous ethical studies, and also research ethics scandals in the past, have indicated that when recruiting participants to clinical trials information has not always been adequate, and that participants have not understood or not received enough information in order to make a rational decision whether or not to participate.[1–5] Also, in order to improve the quality of information provided to participants, the quantity of information has generally increased.

However, the question now arises whether the pendulum has swung too far in the direction of offering more extensive written information. It is not unreasonable to suppose that the reason for more extensive information does not lie primarily in the interests of potential participants, but more immediately in the indemnification needs of pharmaceutical companies. A task for medical ethicists is to find ways of getting medical researchers seriously interested in ethical issues, so as to reflect on the optimal use of informed consent without simply following the trend in the commercial sector.

FROM AN ETHICAL PERSPECTIVE, IS MORE INFORMATION ALWAYS BETTER?

In clinical research, especially when a pharmaceutical product is on trial, the trend in procedures has been towards more and more information. Ever more aspects (including the nature of commercial ties, property issues, conflicts of interests, and so on) are qualitatively defined as ''adequate information'', and the quantity of information actually made available has subsequently increased. Influenced by, for example, the US Food and Drug Administration and similar European research regulating bodies, the pharmaceutical companies have covered more issues and provided more and more details in the name of ''good clinical practice''.[6–8] It is not unusual to see information leaflets to potential participants comprising 4–8 densely written pages, and sometimes even more. In the case of biobank based research, for example, where it was not normal to offer any information at all to donors 15 years ago, research institutions have begun sending out between one and five pages on a project on the basis of stored samples.[11] In such cases, it appears that the offer of more information is perceived by the research institution to represent better research ethics.[11] The increase in the information made available is justified by reference to a duty to provide participants with the opportunity to make rational decisions, thereby respecting their autonomy.

Apparently, it is reasonable for some research institutions to assume that the more you are informed, the better is your basis for decision making and self protection. It is also possible to find empirical support for the view that participants prefer detailed and more extensive, rather than less detailed and restricted, information.[9] As potential participants and responsible citizens, we are supposed to read an information sheet, to understand the information, to consider the pro and cons, and then come to a rational decision. Most medical ethicists would probably question whether the axiom—the more information, the better the ethics—is always applicable in real life. Empirical studies, however, have also shown that a brief information sheet gives rise to greater comprehension and recollection than a longer one.[10] The information in a long sheet can become far too detailed, and accordingly counterproductive. Also, some studies indicate that participants consent to participating without even having read the text provided.[11–13] They trust in the research institution, and sometimes simply refrain from reading the many pages of information.[14] In cases where people abstain partly because the information sheets are too long or detailed, maximising the quantity of information might even contribute to uninformed subjects being unable to assume responsibility for their own participation. If a researcher wants potential subjects to use the information

available and take part in decision making, the quantity, quality, and formatting of the information must reflect the interests and competencies of potential participants. Some assimilate written information better than oral, others vice versa; some request technical details, whereas others do not; some feel anxious when asked to take part in decision making, and need to be addressed differently from participants eager to make their own decision.[15–17] The question is how to make medical researchers with little training in research ethics alert to the individual needs of research participants. How should medical ethicists make scientists reflect on the possibility that either too little or too much information is suboptimal?

A PROPOSED PEDAGOGICAL MODEL

We suggest, as a pedagogical model for ethics training, that the quantity, quality, and formatting of information might be understood by analogy with the logarithmic based dose response relation in pharmacology and other subject areas (see fig 1). In what follows, we presuppose that the information provided contains all the adequate and comprehensible data necessary for decision making, but also encompasses information of minor importance not essential to making a rational decision.

When quantity of information increases (ceteris paribus), the response will increase but only within a certain interval. In relation, for example, to pharmacological dose response curves we refer to therapeutic intervals (TIs) (see fig 1). A TI is an interval where a certain dose is proportional to a certain response regarding a biological variable (the pharmacokinetics of a certain individual). Pharmacological dose response curves are usually based on a drug receptor binding model, where the variance between low and high concentrations of a drug is related to response. For example, enzyme activity might influence physiological reactions, such as heart beat or blood pressure. Since variation in concentration may range from 1 to 10 000 nanomolecules the dose measure is converted logarithmically (1 becoming 10; and 4, 10 000). In the case of quantity of information, the number of words may also vary. The point is that a certain patient may have a very quick pharmacokinetic reaction, based on his or her specific enzyme system, whereas other patients may react very slowly. Thus, the first group of patients should receive more of the prescribed medicine, whereas the latter group should receive less. By analogy with the TI, we can also speak of an *effective interval* (EI) when dealing with quantity of information. In this context, optimal information means that participants receive neither too little nor too much information. When a dose (in pharmacology) lies beyond the TI, the therapeutic effect tends to disappear, with side effects or direct harm to the patient as a result. Similarly, it might be the case that when quantity of information increases to a certain extent, the main message tends to get drowned in detail; in the worst case, participants refuse or are incapable of assimilating the information. Accordingly, the written information provided does not influence the decision, which instead is based solely on, for example, trust in researchers or the healthcare system. Hence, too much information might be counterproductive in relation to the type of choice that informed consent is supposed to facilitate, and also negates the control function that the consent requirement is designed to effect in relation to research.

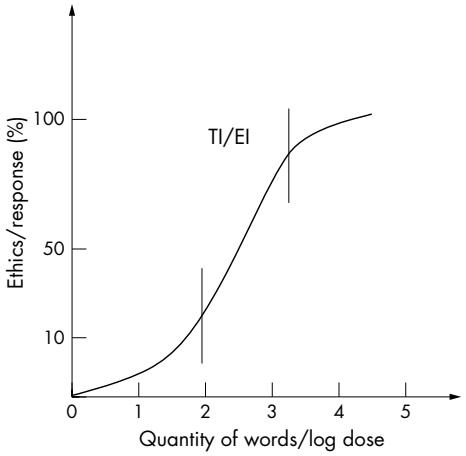

Figure 1 A proposed dose response curve in which quantity of words is transformed onto a logarithmic scale (for example, 2 means 100 words, and 4 means 10 000 words). In a medical context, the shape and slope of the curve vary according to type of disease and other circumstances. In the current setting, we suggest use of the therapeutic interval (TI) or effective interval (EI), where information is assumed to be optimal with regard to the length of the sheet of information received.

Medical students' in-depth understanding of pharmacology, and their adjoining respect for the dose response curve, might in this way be used to enhance both the student's and the medical research institution's attentiveness to the individual needs of potential research participants with regard to quantity, quality, and formatting of information, and thus help overcome simplified maxims of the type ''more information equals better ethics''.

Further, using the dose response curve as a point of departure for future empirical studies in the field of ethics, we might be able to discriminate between different shapes and slopes of the curves in relation to different diseases, conditions, and other relevant factors. Thereby, it might be possible to provide tailored written information to individual patients, at least in terms of providing a briefer or a more extensive version according to individual preference.

CONCLUSION

In many European and North American research institutions the pendulum seems to have swung from providing participants with too little information to providing them with too much—both strategies resulting in suboptimal information practise. Although oral information might be tailored to the individual participant, the dose response model might have the pedagogical potential of estimating the quantity of written information required by participants in clinical trials. Also, the analogy might serve as a framework for interpreting empirical studies of potential participants' reactions to various consent procedures.

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