Towards evidence based bioethics

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Use of epidemiological methods to study human behaviour is necessary to create an evidence base to inform ethical positions in medicine and science

Bioethics has to date largely consisted of analyses of the moral underpinnings of appropriate behaviour in science and medicine. Although such theoretical writings often make important contributions to public health, they often contain unfounded assumptions about human behaviour. I describe recent examples in which assumptions made in theoretical writings were later repudiated, or in which empirical work served further to clarify positions taken in theoretical pieces. Paralleling the rise of evidence based approaches to clinical medicine, these examples show that further emphasis on empirical analysis is needed to promote more balanced, and evidence based, bioethics.

In 1988 Benjamin Freedman noted that perception, rather than reality, controls the generation and resolution of ethical issues.¹ Writing during the first decade of the HIV/AIDS epidemic, he was referring to how the debate on doctors' duties to render care to AIDS patients was influenced by doctors' perceptions of the risk that patients might transmit the virus to them, rather than the actual risk conferred, which was not yet known. In the absence of evidence, intuition and perception have useful roles.

But what ought to guide ethical deliberations once evidence becomes available? Although evidence emerged that the risk of HIV transmission from patient to doctor is extremely low,^{2,3} resolution of many doctors' fears lagged behind and perception led several doctors to continue refusing to treat patients infected with HIV. I argue that, although Freedman correctly noted that perception often controls the generation as well as the resolution of ethical issues, this statement is only half true when placed in the normative realm: perception ought to govern the generation of ethical issues, but reality must often govern their resolution.

The rise of evidence based medicine

Traditional medical teaching held that clinical experience, observation, and acumen would lead to optimal care for patients. Although these remain laudable goals, we now know that seemingly logical clinical insights may turn out to be seriously flawed when scientifically scrutinised. Two examples from the cardiovascular literature will illustrate the point.

In the 1950s, several cardiologists and surgeons logically presumed that they could improve the quality of life of patients with angina pectoris by shunting a greater percentage of the cardiac output through the coronary vessels. Surgeons began ligating the internal mammary arteries to force more oxygen rich blood to the myocardium. The belief that this would ameliorate chest pain was supported by early case series, in which patients experienced both symptomatic relief and improvements in exercise tolerance postoperatively. However, when the procedure was tested in a randomised trial comparing arterial ligation and sham

surgery (in which the skin on the chest was incised but the arteries left intact), it quickly became evident that the benefits of the procedure were no greater than those obtainable with the surgical equivalent of a placebo.^{4,5}

A second example concerns the proper management of patients with myocardial infarction. Cardiologists, noting that ventricular arrhythmias represented the most common cause of death immediately after myocardial infarction, reasoned that administering drugs to suppress these arrhythmias should improve survival. Testing this sensible theory in a placebo controlled trial yielded a disconcerting lesson: not only were class Ic antiarrhythmic agents ineffective, they were actually associated with an increased risk of death.⁶ Doctors soon accepted both sets of results; arterial ligation and postinfarction class Ic antiarrhythmic drugs were quickly eliminated from our therapeutic armamentarium.

Errors in bioethical theory

Just as these examples highlight changing evidentiary standards in clinical medicine, a similar transition is needed in bioethics. Consider the ongoing debate on the ethics of paying patients to participate in research studies. Many ethicists have argued that paying research subjects represents an undue inducement—"undue" because financial incentives may alter patients' decision making processes such that they will not appropriately consider the risks of participating.⁷⁻¹² If payment blinded patients to the risks of research participation it would preclude patients from granting fully informed consent and thereby violate their autonomy.

Although it was reasonable to assume, a priori, that payment represents an undue inducement to participate in a trial, two recent empirical studies have found no evidence to support this concern. In the first study, my colleagues and I investigated the willingness of 126 hypertensive patients to participate in placebo controlled trials of experimental antihypertensive drugs.¹³ Using a 3×3 within subjects factorial design, in which we varied risk level and payment and presented each patient with all nine possible combinations, we found that patients' valuations of the importance of risk were not attenuated at higher payment levels.

In the second study, Bentley and Thacker studied the willingness of 270 healthy pharmacy students to participate in various randomised trials in which the severity of risk and monetary inducement were similarly varied.¹⁴ Using a different method—a 3×3 between subjects design, in which each participant was randomly assigned to receive only one scenario—these authors found almost identical results to our own. In both studies, increasing levels of payment and decreasing levels of risk were each associated with increased

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willingness to participate, but the effect of risk was similar across payment levels (although both studies were specifically powered to detect such effect modification if it existed).^{13 14}

Ethicists have also argued that the influence of financial inducements may be particularly strong among poorer members of society,¹⁵ and that this disproportionate influence may unjustly persuade one segment of society to participate in trials that may benefit all. This argument too has been proffered without any evidence regarding the extent to which the concern manifests—it was not known whether patients with different incomes were differentially influenced by set payments. In the same study described above, we investigated this second question by comparing the responsiveness of more and less wealthy patients to increasing payment levels.

Surprisingly, we found that patients with incomes above the median were influenced by higher payments to a significantly greater extent than patients with incomes below the median.¹³ When asked to explain why their willingness to participate did or did not change with increasing payment levels, poorer patients were more likely to make statements such as “Money doesn’t mean anything when it comes to your health.” Taken together, these results undermine many of the theoretical challenges to the practice of paying research participants.

Evidence has countered ethical theory in other situations as well. Beauchamp and Childress reviewed how ethicists and state legislatures have supported the “reasonable person standard” (in which the amount of information disclosed is expected to meet the requests of any reasonable person) to guide the appropriate type and amount of information disclosure in seeking informed consent, although evidence shows that patients often make decisions before and independent of the process of receiving information.¹⁶ Citing studies of patients making decisions on family planning, kidney donation, endoscopy, and breast cancer therapy, these authors argue that evidence has cast doubt on theoretical arguments for what should count as adequate disclosure to patients. As another example, Roberts described how observational studies of decisional capacity and risk assessment among patients with mental illness should serve to alleviate prior theoretical concerns about the ethics of research among such patients.¹⁷

More balanced bioethics

Theory must certainly maintain a prominent role in bioethics. Elucidating the moral justification for appropriate behaviour provides compelling guidance for our actions. Furthermore, innovative theories and arguments are critical for ethics to advance. For example, the persuasive writings of Kant and others, on how individuals have the right to self determination, have largely spurred the recent democratisation of medicine and increase in respect for patients’ autonomy in guiding their health care.^{18 19}

Unlike the original theories, that paying research subjects represented undue or unjust inducements, this principle of respect for autonomy does not presuppose any empirically verifiable claims and so is not subject to repudiation by evidence. However, because understanding this principle does not allow us to determine

Summary points

Bioethical theory often rests on unproved assumptions about human behaviour

Empirical analyses can document the extent to which ethical concerns manifest in reality and can identify ways in which these concerns can be mitigated

Theoretical and empirical approaches can work synergistically to promote more balanced bioethics

how much autonomy in making decisions patients want, which models for shared decision making work best, or how doctors ought to be trained to make these models work, an important role remains for the series of studies aimed at understanding this issues.^{20–22}

Theoretical and empirical approaches therefore may work synergistically in different ways. In the case of paying research participants, the original theoretical arguments identified the potential for ethical problems; empirical studies later showed that these problems do not manifest as was assumed; and more recent theoretical work has incorporated this evidence into a refined discussion of the issues.²³ In the case of disclosing information as a means of respecting autonomy, a primary ethical principle was established, and evaluations of its implementation have indicated the need for new strategies to uphold this principle.

Conclusion

There will always be a need for thoughtful writing about social and philosophical perspectives on clinical care and biomedical research. Such theoretical writings place our practices as doctors and investigators into appropriate contexts and provide constant checks to ensure that these practices are responsive to changing circumstances. Furthermore, many timely issues are not amenable to scientific investigation and instead require persuasive theoretical arguments so that change can be implemented. In cases where investigation is possible, however, “position pieces” that rely on as yet unverified claims should be viewed as hypothesis generating until the claims are properly evaluated, just as early experimental results must await confirmation by larger studies before being accepted. Applying this scientific method to bioethics—thereby creating more evidence based bioethics—will serve our patients, research participants, and profession best.

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Statistics Notes

Standard deviations and standard errors

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The terms "standard error" and "standard deviation" are often confused.¹ The contrast between these two terms reflects the important distinction between data description and inference, one that all researchers should appreciate.

The standard deviation (often SD) is a measure of variability. When we calculate the standard deviation of a sample, we are using it as an estimate of the variability of the population from which the sample was drawn. For data with a normal distribution,² about 95% of individuals will have values within 2 standard deviations of the mean, the other 5% being equally scattered above and below these limits. Contrary to popular misconception, the standard deviation is a valid measure of variability regardless of the distribution. About 95% of observations of any distribution usually fall within the 2 standard deviation limits, though those outside may all be at one end. We may choose a different summary statistic, however, when data have a skewed distribution.³

When we calculate the sample mean we are usually interested not in the mean of this particular sample, but in the mean for individuals of this type—in statistical terms, of the population from which the sample comes. We usually collect data in order to generalise from them and so use the sample mean as an estimate of the mean for the whole population. Now the sample mean will vary from sample to sample; the way this variation occurs is described by the "sampling distribution" of the mean. We can estimate how much sample means will vary from the standard deviation of this sampling distribution, which we call the standard error (SE) of the estimate of the mean. As the standard error is a type of standard deviation, confusion is understandable. Another way of considering the standard error is as a measure of the precision of the sample mean.

The standard error of the sample mean depends on both the standard deviation and the sample size, by the simple relation $SE = SD/\sqrt{\text{sample size}}$. The standard error falls as the sample size increases, as the extent of chance variation is reduced—this idea underlies the sample size calculation for a controlled trial, for

example. By contrast the standard deviation will not tend to change as we increase the size of our sample.

So, if we want to say how widely scattered some measurements are, we use the standard deviation. If we want to indicate the uncertainty around the estimate of the mean measurement, we quote the standard error of the mean. The standard error is most useful as a means of calculating a confidence interval. For a large sample, a 95% confidence interval is obtained as the values $1.96 \times SE$ either side of the mean. We will discuss confidence intervals in more detail in a subsequent Statistics Note. The standard error is also used to calculate P values in many circumstances.

The principle of a sampling distribution applies to other quantities that we may estimate from a sample, such as a proportion or regression coefficient, and to contrasts between two samples, such as a risk ratio or the difference between two means or proportions. All such quantities have uncertainty due to sampling variation, and for all such estimates a standard error can be calculated to indicate the degree of uncertainty.

In many publications a $\pm$ sign is used to join the standard deviation (SD) or standard error (SE) to an observed mean—for example, 69.4 ± 9.3 kg. That notation gives no indication whether the second figure is the standard deviation or the standard error (or indeed something else). A review of 88 articles published in 2002 found that 12 (14%) failed to identify which measure of dispersion was reported (and three failed to report any measure of variability).⁴ The policy of the *BMJ* and many other journals is to remove $\pm$ signs and request authors to indicate clearly whether the standard deviation or standard error is being quoted. All journals should follow this practice.

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