HTA decision-making: Do ethics matter?

Art Gertel
MedSciCom LLC, White House Station, NJ, USA

Correspondence to:
Art Gertel
medscicom@rcn.com

Abstract

Before reviewing the article in this issue of *Medical Writing* by Larry Liberti and Tina Wang, *The regulatory-HTA decision-making interface: What the medical writer should know* (p. 50), I put on my ethicist's hat. Thus, I tuned my ethics antennae to detect whether there might be some concerns about issues that could result in unintended harm, either to individual patients, or to the collective society to which health technology assessment (HTA) and regulatory authority decisions might apply. I approached the evaluation as an opportunity to ask questions that should be considered, rather than suggest solutions. This may better enable those charged with making critical healthcare decisions to evaluate choices in context, rather than attempt to apply overarching "rules". This approach, of course, raises the challenge of whether it is appropriate to apply "situational ethics", or whether there should, indeed, be universal standards that should remain inviolable and absolute. Perhaps, this is where objective algorithms must be melded with subjective human assessments, based on education, experience, expertise, personal values, and instinct. Hopefully, this will stimulate thoughtful questions in the context of HTAs, and medical writers will better understand the scope of medical decision-making. In this way, we may raise awareness, and hopefully, prevent – or at least recognise – the potential for harmful unintended consequences of certain HTA-based medical decisions.

The EUnetHTA HTA Core Model

The International Network of Agencies for Health Technology Assessment (INAHTA) Working Group on Ethical Issues has identified and defined various methodological approaches that are used by HTA agencies.[1] The European Network for Health Technology Assessment (EUnetHTA) HTA Core Model (version 3.0), mentioned in the article by Liberti and Wang,[2] recognises ethical aspects of health technologies, which should be considered in an HTA Core Model. As noted in this document, "Ethics … has a broader application within the field of HTA. The assessments themselves should be designed in such a way that key ethical principles are considered and respected". EUnetHTA also raises an overarching question of whether there are ethical issues related to the consequences of performing the HTA.

These principles reflect the protection of human rights first established by the Nuremberg Code (1947),[3] and progressively embodied in subsequent declarations, including the Declaration of Helsinki (1964, updated most recently in 2013);[4] The Belmont Report (1974);[5] and Regulation (EU) No 536/2014 of the European Parliament and of the Council (2014).[6] In addition, the International Council of Harmonisation (ICH) has embodied many of these principles into their Good Clinical Practices guidance.[7,8]

In each case, there are six primary principles that should be evaluated:

1. Benefit-harm balance
2. Autonomy
3. Respect for persons
4. Justice and equity
5. Legislation
6. Ethical consequences of the HTA

In reviewing these principles, it is important to keep four key concepts in mind:

1. The ethics of product vs. the ethics of process
2. The interests of the individual patient vs. the interests of society
3. The differences between practice and research
4. The economic vs. therapeutic value

It is important to recognise that there may be inherent conflicts (or at least, dynamic tensions) in attempting to satisfy both considerations in each of these examples. Thus, in evaluating applications, questions arise concerning these concepts, all of which may be applied in the assessments:

- What are the trade-offs between the benefits to the patient vs. those to society?
- Should approval or denial of funding new therapies be based on cost alone?
- Are end-of-life years more or less valuable than those at earlier stages?
- Should negative or inconclusive data be considered when one believes that these data may represent an exception?
- Is there a risk of decision-maker bias, incorporating *a priori* assumptions about the interventions being evaluated, as well as the understanding of the HTA goals?

While I will not address all of the aspects mentioned above, I have selected those topics that I believe are most germane to the medical writer.

Benefit-harm balance – accelerating access to new therapies and vaccines

These are strange times, and in the midst of a pandemic, the "normal" standards of proof and determination of the benefit-harm balance may have to be adjusted. Liberti and Wang note that *"a new challenge has emerged with the preponderance of new innovative products that are receiving regulatory authorisation where there is an unmet medical need, and therefore, few therapeutic alternatives. Using facilitated regulatory pathways (FRPs) such as the breakthrough therapy designation, priority and accelerated reviews, and conditional marketing authorisations, important new therapeutic options with good signals of clinical efficacy are being approved in record times"*.[2] This has come into sharp relief in the context of the COVID-19 pandemic. I have previously written about the potential harms associated with some forms of pre-approval access, most notably, those associated with pathways facilitated by the Right-to-Try Act in the USA, and the Saatchi Bill in the UK.[9]

As Liberti and Wang state, "… *the paucity of long-term data – and therefore the reliance on surrogate endpoints for the regulatory decision – make formulating a value recommendation complicated*".[2] I certainly agree, and we must confront concerns, in the context of desperation, about whether some of the standards of empirical research should be compromised, in the interest of making potentially life-saving therapies and vaccines available earlier than they might be otherwise. Furthermore, we must confront such concerns with an acknowledged acceptance of the potential for increased risk (primarily due to the "unknown unknowns") assumed when we "lower the bar". Is it legitimate to create "one-off" regulatory standards? What are the consequences? In this context, how are the probability of harm and possibility of benefit adequately conveyed in informed consent, when the testing process has been accelerated? How will we communicate to the public and prescribers about therapies/ vaccines that have been "approved" based on lower standards?

This raises the topic of "situational ethics". Do desperate times require desperate measures? Is "no science" worse than "bad science"? In this time of great global peril, when countless lives are being held in the balance, are we willing to lower the threshold of scientific integrity for the sake of accelerating the availability of speculative medicinal products?

These compromises may even occur outside of the context of a pandemic, as demonstrated by the recent FDA approval of aducanumab for Alzheimer's disease.[10] In my opinion (and that of the independent advisory committee) the evidence that its manufacturer, Biogen, submitted to the FDA showed no convincing effect on patients' cognitive decline. Its two main trials were stopped early in 2019 because Biogen concluded that its drug did not work. Reanalysis, using questionable surrogate endpoints based on a putative association between myeloid plaque levels and cognitive function, resulted in approval, despite concerns about brain swelling and haemorrhage associated with higher doses of the drug. Thus, there are issues of raising false hope in patients and their families, thereby increasing risk; and given the high cost of the drug (monthly infusions with a US$56,000 annual price tag, and the need for regular MRI scans to monitor for brain swelling), an added financial burden.

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There is no question that bad science does not deserve a forum. However, good science needs to be heard, even if some people will twist its meaning. Hopefully, scientists desire the safest and most effective treatment or vaccine and the most reliable diagnostic possible, but these cannot be refined if researchers ignore inconvenient data. Moreover, scientists will earn a lot more public trust, and overcome a lot more unfounded fear, if they choose transparency over censorship. As Jacci Parsons[11] points out in her article, "The key aspect of all forms of communication of results is transparency. This is especially true for uncertainty, as it is more difficult to communicate and more difficult to understand than simple 'results'". After all, research is a building-block process. There is no crystal ball into which we may gaze to determine absolute truth. Technological advances and human insights will open the doors to a better understanding of processes that had been hidden from us in the past.

Even in the traditional course of research, development, and approval of novel therapeutics, there are often late-emerging untoward sequelae – signals that emerge only after a drug has been commercially available and administered for years after approval. One needs only recall Pfizer's withdrawal of Bextra from the US market on recommendation by the FDA, citing an increased risk of heart attack and stroke, as well as the risk of a serious, sometimes fatal, skin reaction. Other examples include Zelnorm, withdrawn based on evidence that it raised the risk of heart attacks and strokes; and ketoconazole-related cardiac arrhythmias associated with Seldane and Hismanal, resulting in the addition of "black box" warnings to their product labels. It is interesting that the majority of cases of product withdrawal are due to cardiovascular safety concerns.

In the context of designing a clinical trial, should benefit-harm ratios be established when considering comparators? If the benefit-risk ratio falls below a certain threshold, should the patient be allowed to be treated with the investigational product?

Autonomy

Overlaying this discussion is the principle of individual agency – the capacity for human beings to make choices and impose those choices on the world. This should be distinguished from the concept of "free will", as these choices are not to be influenced by outside forces. This is important in determining the degree of protection from undue influence in making critical healthcare decisions. Of course, we are not computers, driven by algorithms, and there will always be a

degree of influence, sometimes to our benefit. For example, it is wise to seek counsel of a "learned intermediary", who may be well-versed in the complexities of a particular disease and its treatment options. This subject matter expert may then serve as an advocate or adviser. Human agency invests a moral component into a given situation. If a situation is the consequence of human decision-making, persons may be under a duty to apply value judgements to the consequences of their decisions and be held responsible for those decisions. This concept applies to societies as well as individuals. Governments have the ability to make decisions about what they believe is best for their citizens, and by extension, the world. Sadly, political considerations will almost always colour these decisions.

Another aspect is the exercise of autonomy by clinicians, in terms of accepting what may be limited data, including some that may be anecdotal. There are very clear distinctions between medical practice and medical research, and these may not be clearly understood by patients, and in many cases, clinicians. These have been articulated in the Belmont Report.[4] Practice consists of "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioural practice is to provide diagnosis, preventive treatment, or therapy to particular individuals". Research is an "activity designed to test a hypothesis, permit conclusions to be drawn, and thereby, to develop or contribute to generalisable knowledge. Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective".

How do, or should, we counter the tendency to believe in information based on sub-standard sources (e.g., those for which no solid empirical evidence exists)? Are the "gold standard" randomised, controlled, clinical trials a required evidentiary standard in the teeth of a pandemic?

Decision-making

In the previous section, I addressed the quality of data used to make the critical decisions facing regulators, HTAs, physicians, and patients. One might first consider a hierarchy of "admissible evidence", based on legal concepts applicable to a court of law:

Anecdote ▶ Data ▶ Evidence ▶ Admissible evidence

Anecdotes are unstructured. Data have structure but may contain irrelevant or misleading information. Evidence requires an analysis of the data with an objective of proof. "Clear evidence is positive, precise, and explicit, as opposed to ambiguous, equivocal, or contradictory proof, and which tends directly to establish the point to which it is adduced, instead of leaving it a matter of conjecture or presumption, and is sufficient to make out a *prima facie* case".[12]

Decisions are often made without applying rigorous decision-making tools, such as the 8-step medical/regulatory decision-making tool, the Universal Methodology for Benefit-Risk Assessment (UMBRA), developed by the Centre for Innovation in Regulatory Science (CIRS).[13] However, even when such tools are used, much of the process allows for subjective input by individuals involved in the process of weighting and grading of factors, which are used to guide decision-making.

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Newly evolving studies of the neurocognitive bases for decision-making may shed further light on how we might improve the processes and outcomes associated with critical decisions. This research may be particularly valuable, as it incorporates economics into the paradigm. In the context of the HTA, where consideration is given not just to the therapeutic profile, but the economic impact of reimbursement, this might have meaningful consequences.[14] As noted in Wendy J. Babidge's article,[15] in this issue of *Medical Writing*, (see p. 16) companion concepts include increasing reliance on evidence-based medicine, real-world data (RWD), and real-world evidence (RWE).

Justice and equity – individual vs. society

At the outset, it is important to recognise that, at the interface of institutional healthcare decisions, there will often be a dynamic tension between the individual patient and society. This often is a result of limitations on resources – financial, therapeutic, and personnel – which must be drawn upon to serve the needs of citizens. Thus, all needs of all people can seldom be met, and this means that the calculus of "the greatest good to the greatest number" will usually be applied.

Perhaps the most relevant issue with respect to justice and equity, aside from ensuring that there is no discrimination in the availability of healthcare, based on socioeconomic or racial characteristics, is the fundamental dynamic tension between the individual and society. There are, necessarily, trade-offs between potential value to be gained by each of these entities. Thus, one must consider if, as an individual member of society, one has an obligation to the greater good of the greater number of that group to which one belongs. This concept applies to both personal obligations and personal liberties. We obey laws and societal conventions, not because they necessarily have great potential benefit to us (not robbing the local bank, for example), but because they form the underpinnings of a functioning society. We also have protective laws in place that constrain unwarranted actions by society (e.g., laws against illegal search-and-seizure).

Likewise, governmental agencies, which provide the funding (via taxpayers, of course) for healthcare – including reimbursement for the cost of drugs – must consider themselves stewards acting on behalf of both individuals and groups within their citizenry. Fundamental economics stipulate that there are not enough resources to serve all the needs of each citizen, resulting in the need to make difficult decisions about where to allocate funds that provide the optimum affordable coverage. In a sense, this runs counter to situational ethics, in that there are few opportunities, let alone capacity, to consider individual cases on their own merit. Thus, more generalisable solutions, which are often algorithm-based, must be applied.

Reimbursement

Another major consideration is that HTA bodies and payers are investigating novel approaches to reimbursement, including concepts such as coverage with evidence development, cost sharing, and price-volume agreements. As explained in an article in this issue by Michael Köhler and Annette Christoph,[16] (p. 22) early benefit assessment in Germany provides publicly available, comprehensive information – in both scientific

and easily understandable formats – on the added benefit of new drugs.

Given that there is a tendency to rush access to potentially valuable therapeutics and vaccines through Emergency Use Authorizations (EUAs) in the US, and Conditional Marketing Authorisations (CMAs) in the EU, will reimbursement schemes be modified, based on emerging data – which might include a lack of long-term efficacy/safety? The WHO resolution on HTA states that most HTAs should be focused on the domains of safety and effectiveness, and then economic/budgetary areas, with much less emphasis on aspects of ethics, equity, and feasibility.[17]

Are there inherent conflicts of interest between regulators and health technology assessors? Do they really share common goals? Is there incentive for cost containment on the part of profit-driven pharmaceutical companies? Historically, commercial approval occurs first, followed by allocation of reimbursement funding. Given the pressures due to urgency, will these two decisions now occur in parallel? If a high-cost therapeutic regimen proves anecdotally effective (à la initial reports regarding hydroxychloroquine and unrestricted use of remdesivir in COVID-19 patients), should the therapy be made available to the public at large? Who should pay for it?

Concluding thoughts

Ultimately, healthcare decisions – whether to approve a drug, device, or vaccine for commercial use or emergency use, and how to cover the costs – rely heavily on human factors. We cannot afford to assess individual cases of need on their situational merits, and therefore, must apply tools that will, by their very nature, be imprecise, imperfect, and uncertain. We cannot avoid influences, whether well-intentioned or malign. All we can do, as both individuals and society, is look after each other and try to ensure that protective ethical standards are in place, unintended consequences are considered, and knowledge is not fixed. It is an evolving process. Ethics DO matter.

Disclaimers

All thoughts and opinions expressed in this article are the author's own.

Conflicts of interest

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Author information

Art Gertel is the Principal of MedSciCom, LLC – a strategic regulatory consultancy, based in the USA. He also teaches and writes about bioethical issues in the context of clinical research. Art is a past president of the American Medical Writers Association (AMWA) and is a Fellow of both AMWA and EMWA.