

Correspondence

Medical Decision Making: The Family–Doctor–Patient Triad

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The importance of a person-centred approach and the intricacies of risk communication have recently been well described in *PLoS Medicine* [1,2]. The applicability of the patient-centred approach to Eastern countries, however, has cultural, religious, and practical impediments that demand careful consideration. The bulk of the world population lives outside the United States and western Europe. Unlike in the West where the patient takes centre stage by both tradition and law, the family–doctor–patient triad is the norm in Eastern states, in general, and Pakistan in particular [3–8].

Pakistan is a predominantly Muslim country of 150 million people. About half the population is uneducated, and more than a third lives below the poverty line. There is one doctor for every 1,432 patients, compared to one doctor for every 390 patients in the US. The health-insurance system is virtually nonexistent, and there is no concept of assisted-care living, with the care of the elderly largely taking place at homes by their families. Strongly held religious beliefs and cultural views govern everyday life and dictate the roles of every member of the society. Families consist of well-knit, supportive, and collectively earning interdependent members who take mutual decisions on all matters pertaining to life and death [3,4]. The elder members of the family command the greatest respect and authority. The family unit is the functional unit of the society, the dynamics of which need attention and respect.

Strong family systems and the authoritative position of the doctor are the governing forces of medical decision making in these countries. Illiteracy, poverty, poor awareness of patient's rights, and a lack of accountability for physicians are factors conducive to such a practice. With this background, the role of the patient is limited. Health expenditure is borne by the family, giving it a central role in decision making. The concept of the financial survival of the family is a harsh reality [3,4]. The health-care costs of one seriously ill member may jeopardize the survival of others by draining the limited resources. Due to familial, moral, and monetary support, the patient relinquishes the responsibility of decision making and gives the primary role to the family or the doctor. Women, for example, may not give consent unless they get approval from their spouses [5]. In the case of women, who may have a lesser say in the patriarchal family system, the doctor should strive for active participation. Sometimes the family aims to protect the patient from stress by withholding information, and in terminal illnesses, the doctor and family act in concert to conceal complete information from the patient. They, for example, may not mention the word cancer to patients who have malignancies [9].

In contrast to Western practice, the role of the doctor is authoritative. Doctors are regarded as instruments of God and given the final authority in decision making [3,4,10]. In such circumstances, doctors are likely to take decisions unilaterally. When they do involve patients in decision making, physicians accept the centrality of families, with

some considering patients and families as one [5]. One worry regarding communication of harm is of losing patients to other physicians with a more reassuring “nothing will go wrong” attitude [5]. It is also said that more time and patience are required to explain things to the illiterate. It is perhaps impractical, therefore, to expect overworked and underpaid physicians to practice risk communication according to the book.

Thus, the concept of individual centrality that is so elementary in the West stands challenged in the East. Research is needed to formulate appropriate strategies of risk communication. Areas needing research include the patient's concept of autonomy, the role of the family as perceived by patients and doctors, the existing practices of medical decision making, and the training of doctors in communicating risk.

An economically sound and literate population, properly trained doctors, and institutional checks and balances are essential prerequisites for establishing decision making with parity of partners. The need is to find a middle ground where not only the family unit is respected, but the patient also plays a proactive role. A dynamic balance between cultural values of caring and the possibility of a more individualistic role in health care is needed and is, indeed, attainable. Doctors, being the most influential component of the family–doctor–patient triad, can play a significant role in bringing about this change. ■

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Citation: Aslam F, Aftab O, Janjua NZ (2005) Medical decision making: The family–doctor–patient triad. *PLoS Med* 2(6): e129.

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Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020129

Malaria Diagnosis and Treatment: One Size Does Not Fit All

Chris Drakeley, Roly Gosling, Hugh Reyburn

Icke and colleagues highlight an online and CD-ROM source available for the teaching of malaria diagnosis [1]. While this is a commendable initiative that provides open access to badly needed training materials, we feel that it is overambitious to propose this Web site (which gives equal weight to diagnosis, treatment, and chemoprophylaxis) as a resource that can be equally relevant to the issues of travel-related malaria, to which the Web site primarily applies, and the problems of malaria diagnosis and treatment in sub-Saharan Africa, which are described as the primary focus in the *PLoS Medicine* article [1].

The microscopic diagnosis of malaria is indeed an important resource in Africa to which the large majority of health facilities do not have access. Even where microscopy is available, there is evidence of substantial overdiagnosis of malaria and that better access to malaria microscopy may not result in better targeting of antimalarials [2,3]. What data there is on the accuracy of slide results suggest that microscope quality, preparation of blood films, and quality of reagents are at least as important in constraining the quality of results as the ability of slide readers to identify *Plasmodium* parasites from high-quality thin blood films [4–6]. In fact, thick blood films are the norm in Africa, thin films being almost exclusively confined to research, yet these are in the small minority on the Web site.

P. falciparum is overwhelmingly the dominant *Plasmodium* species seen in Africa, and training guides that try to give a “global overview” run the risk of giving a misleading impression of the relative importance of the four species in any given setting where malaria is endemic. The only actual setting where all species of malaria might be seen relatively frequently would be in travel clinics in developed countries. This point might seem obvious, but for many junior laboratory technicians in Africa hungry for scarce training opportunities it is potentially distracting and confusing.

The problems of simultaneously addressing the issues of malaria in endemic areas of Africa and in travellers from resource-rich countries are particularly applicable to malaria treatment. On the Web site, among the drugs recommended for the treatment of non-severe malaria are quinine, atovaquone/proguanil hydrochloride, mefloquine, and two tetracyclines. In Africa quinine is reserved for severe malaria and is associated with a high rate of failure due to poor adherence in outpatients; atovaquone/proguanil hydrochloride and mefloquine are not widely used because of their high cost; and tetracyclines are contraindicated in children and pregnant women, who bear the overwhelming burden of malaria.

The Web site describes criteria for severe malaria that are not appropriate for Africa. Thus, cerebral malaria, jaundice, renal failure, and lactic acidosis (impossible to detect in most African hospitals where “respiratory distress” is the equivalent criterion) are all listed ahead of severe anaemia, the most common manifestation of severe malaria in Africa. Repeated convulsions are not mentioned, presumably because they are rare among travellers with malaria, but they are common among children in Africa and are associated

with a poor outcome. Renal failure as a manifestation of severe malaria is mentioned second but is very uncommon in Africa [7,8].

The apparently large numbers of African health-care workers who have accessed this site might legitimately feel confused by some of these descriptions, and there is no indication of which, if any, sections apply to Africa and which to travellers. While many will interpret the information critically, others may not, especially when English is not their first language and where there is a tendency to accept didactic sources in preference to what is obvious from personal or local experience.

The diagnostic component of the Web site has important potential as a training tool, but we feel that significant modification and more explicit indication of information that is country-specific are needed before its use is likely to result in improved standards of care in African hospitals and clinics.

It is true that Internet technologies can “revolutionise information technology...for healthcare professionals in developing countries”. The World Health Organization and others already have very extensive Web sites that are contributing to this. Searching the Internet on “malaria diagnosis” reveals a number of sites, many with excellent sections, but one is struck by the lack of clarity defining the target audience and context of the problem. For much information available on the Web this may not matter, but for malaria we feel it does. ■

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Citation: Drakeley C, Gosling R, Reyburn H (2005) Malaria diagnosis and treatment: One size does not fit all. *PLoS Med* 2(6): e156.

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Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020156

Authors' Reply: Teaching Health Workers Malaria Diagnosis

With reference to the letter commenting on our paper [1] from Drakeley and colleagues [2], they have some justification in stating that one size does not fit all. However our Web site, which is the basis for their comment, was originally designed on a wholly voluntary basis for Australia. We have been overwhelmed by the interest and acceptance of this site worldwide. Not only have we had more than 750,000 visitors to the site but have issued free CD-ROMs to institutions in 149 countries.

The fact that it was warmly embraced by so many others from around the world bears testimony to its usefulness as, indeed, do the tens of thousands of letters and E-mails thanking us for our efforts. We have made some modifications on our annual update in response to suggestions and changes in approach. The main section of interest has been the section on diagnosis, testing, and teaching, and perhaps the reason for this is the high quality of the illustrations. One only has to look at the site to recognize that we have not given equal weight to all sections, as Drakeley and colleagues point out. The emphasis is on diagnosis, testing, and teaching. Many large organizations have requested a substantial number of copies of the CD-ROM, and in Germany one organization has been printing its own (with permission). We are aware of some superb CD-ROMs on malaria put out from other sources, but they are expensive for organizations with a very small budget.

We accept that diagnosis by thick film is the norm in Africa and a number of other countries and, in fact, have spent many years ourselves diagnosing malaria from thick films in India and Southeast Asia. We have described how to make thick films and have provided a picture. We have mentioned the staining of films, but we have not described how to prepare the stains because we considered that outside our brief. It is important with Web sites to be concise, otherwise they won't be read. The actual diagnosis of malaria is the same for Africa, India, South America, and Southeast Asia, and it is the proper diagnosis that we believe is paramount. We know that language can be a serious problem. We have provided a version in French and Spanish. The French version we are told is useful for certain parts of Africa. When other languages have been requested, we have suggested that a small booklet should be written in the local language by those with local knowledge.

In regards to the comments on treatment, this section was written by T. M. E. Davis, who holds the Chair of Medicine at the University of Western Australia and is a consultant on malaria to Thailand and Cambodia. If we sought an expert on treatment for every endemic region, we would never get the material into print. One is not always able to use the drugs of choice in Southeast Asia because up to 50% of antimalarials sold in some areas are fake. It has been stated that children should not be given tetracyclines, but that has already been made very clear on the site.

We are aware that the site needs to take into account various interests and situations, which is why we have included our E-mail addresses on the site. We presume that as experts in the field Drakeley and colleagues would have been aware of the site either in Tanzania or the London School of Tropical Medicine, where a number of CD-ROMs have been requested and sent. We hope and expect that eventually

a group with the enthusiasm of these correspondents will accept the challenge and produce a site that will overcome the problems that are the cause of their concern. We fully understand the difficulty of doing this on a voluntary basis. In the meantime, we will continue to service the site and hope that the very large number of users will continue to find it helpful. Finally, we state once again that if concise suggestions for improvements are sent to us by E-mail we will give them serious consideration. Our E-mail contact is now sandy.treadgold@health.wa.gov.au. ■

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Citation: Icke G, Davis RE (2005) Teaching health workers malaria diagnosis. *PLoS Med* 2(6): e165.

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Competing Interests: To produce and distribute the CD-ROMs discussed in this article, the authors received sponsorship from Becton Dickinson (Franklin Lakes, New Jersey, United States of America) and Abbott Diagnostics (Abbott Park, Illinois, United States of America).

DOI: 10.1371/journal.pmed.0020165

Allocating Antiretrovirals in South Africa: Using Modeling to Determine Treatment Equity

David P. Wilson, Sally M. Blower

Recently *PLoS Medicine* published our paper entitled "Designing Equitable Antiretroviral Allocation Strategies in Resource-Constrained Countries" [1]. We were disappointed to find that the editorial perspective written by the World Health Organization (WHO) ethicists regarding our paper [2] was based upon a substantial misunderstanding of our novel quantitative analyses and our important results. Hence, they misunderstood the significance of the health-policy implications of our results. Thus, we wish to correct the record.

Firstly, Capron and Reis [2] misunderstood our quantitative analyses. They stated that "Wilson and Blower developed a mathematical model that could inform policy-makers' decisions regarding the optimal distribution of treatment sites to ensure equal access by all individuals infected with HIV." However, our model does not determine the optimal distribution of treatment sites. As we clearly state in our paper [1] (and is also stated in the synopsis [3]), we developed a model that policy makers can use to make decisions regarding how to achieve the optimal allocation of scarce antiretrovirals among the available health-care facilities (HCFs) if the objective is to ensure treatment equity. We also calculated how the optimal allocation of antiretrovirals would vary if the number of HCFs utilized increased and/or the size

of the catchment area that each HCF services increased [1]. Thus, we took the treatment sites (i.e., HCFs) as given, and we used their specific spatial location in South Africa as inputs to our model in order to determine optimal antiretroviral allocation strategies under a variety of conditions.

Secondly, Capron and Reis [2] misunderstood our important results. They stated that “applying this tool to the South-African province of KwaZulu–Natal, Wilson and Blower were able to confirm mathematically the intuitive assumption that using a maximum number of centers, at the least possible distance from most affected populations, would lead to the greatest fairness in the geographical distribution of ART [antiretroviral therapy].” We agree that if these had been our results, they would have been trivial and obvious. However, Capron and Reis [2] did not discuss our actual results: we determined how to decide how many drugs to allocate to each of the available HCFs in order to achieve an optimal allocation if the objective is to ensure treatment equity. This is a very complex problem and the antiretroviral allocation strategies that we calculated (by using our model) to be optimal are very complex (see Figure 3 in our paper, which graphically shows the proportion of drugs that should be allocated to each of the available HCFs). Furthermore, we also determined what catchment area each HCF should service; specifically, we calculated that each HCF should serve (if the objective is to achieve treatment equity) a catchment area of 40–60 km. Thus, our results demonstrate (to our knowledge for the first time) that patients infected with HIV will have to travel extremely large distances (i.e., 40–60 km) in order to receive antiretrovirals, if the objective is to achieve treatment equity in South Africa. We stress that currently it is unknown what the actual size of the catchment area is around HCFs in South Africa. Catchment areas may in fact be very small. Thus, we suggested [1] that a primary goal should be to obtain empirical data of the distances that patients in South Africa are willing (or able) to travel in order to receive antiretrovirals. We have been the first to provide a quantitative assessment of the necessary size of the catchment area, and our results have identified that there is an urgent need to collect these critical data for quantifying the size of the catchment areas around HCFs. We have determined that the size of the catchment area will be a critical component in the ability to achieve treatment equity in South Africa. We also compared the optimal antiretroviral allocation strategies that we calculated with the current plan of the South African government for allocating antiretrovirals [4], and we determined that the current antiretroviral allocation strategies in South Africa will not achieve treatment equity. Taken together, our quantitative results are novel and controversial, providing important quantitative insights into a complex public-health problem.

We applaud the ambitious “3 by 5” WHO target for the antiretroviral rollout. However, the WHO has not yet devised a quantitative policy for determining how to allocate antiretrovirals in situations where the demand for drugs greatly exceeds the supply [5]. Health-policy officials in each country will have to make these important and difficult decisions, and they will all make different decisions based upon what objectives they wish to optimize and prioritize. There are a multitude of factors to consider (these factors are well described in the recent *Institute of Medicine* report [6]). We stress that the alternative to a quantitative rational

approach for allocating scarce resources is an ad hoc approach, which is how the scarce supply of antiretrovirals is currently being distributed in many resource-constrained countries. Our operations research modeling approach is based upon spatial heterogeneity in the distribution of HCFs in South Africa and the spatial heterogeneity of the HIV-infected population. The most important “real world” result is that we show that what the South African government is currently doing is inequitable. We show them how to achieve equity, if they wish to do so. We hope that our novel approach for deciding how to allocate antiretrovirals will be of use to the WHO and also to the relevant authorities in the many resource-constrained countries who will soon have to make very difficult decisions as to who lives and who dies. Our analysis is to our knowledge the first analysis to show how a rational and scientific solution can be reached for deciding how to allocate a limited amount of antiretrovirals, if the goal is to achieve treatment equity. Clearly, other goals must be taken into consideration (and our model can be modified to include these other goals); however, we hope that treatment equity will be a very high priority during the antiretroviral rollout that is just beginning. ■

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Citation: Wilson DP, Blower S (2005) Allocating antiretrovirals in South Africa: Using modeling to determine treatment equity. *PLoS Med* 2(6): e155.

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Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020155

Authors' Reply

In response to our commentary [1] on their paper, “Designing Equitable Antiretroviral Allocation Strategies in Resource-Constrained Countries” [2], Wilson and Blower assert that we misunderstood both their analysis and the importance of their results [3]. Rather than “setting the record straight,” what may be needed is more effort to bridge the differences in disciplinary approach that create a greater appearance of disagreement than is actually the case.

On a factual level, we believe Wilson and Blower's results were appropriately described for the purposes of our commentary. As their letter points out, they applied the operations research methods to model the allocation of antiretrovirals (ARVs) among 17 health-care centers in KwaZulu-Natal, based on a hypothetical distribution of HIV/AIDS among the communities in that province. Their article characterizes this as "an elegant and simple theoretical framework," but they object to our concluding that it could "inform policy-makers' decisions regarding the location of HIV services," since they took the treatment sites as given. Yet their article compared the alternatives of using all 54 centers in the province, at one extreme, and of using only a single treatment site (in Durban), at the other extreme; in each case, the possibility of allocating to a larger number of centers is equivalent to the creation of additional centers closer to remote groups of patients.

Wilson and Blower write that geographic accessibility is improved if the number of health-care facilities is increased, and they calculated that it would be optimal if all 54 facilities in the province of KwaZulu-Natal distributed the medicines, instead of just 17. We took this result to confirm the need to reach out and build capacity. We are sorry if we were mistaken in assuming that Wilson and Blower would want to see their stated objective of ensuring fair distribution applied in the real-world context of many poor countries with a high HIV burden and where fairness in ARV care cannot be achieved solely by allocating resources among the existing sites.

A wider gap in perception can be seen in Wilson and Blower's repeated conflation of "optimal," "equal," and "equitable," combined with their suggestion that decision makers who fail to apply their model must be following an "ad hoc approach." The central point of our commentary was that various ethical theories reach very different conclusions about what result would be optimal, and that even among those aiming to achieve the greatest equity (rather than some other optimum), many would not take equality as the measure of equity. Wilson and Blower themselves recognize that apparent equality of access (in terms of distance to treatment) needs further study to determine whether patients can in fact access treatment. We need to know whether some distances are simply too far for patients to travel for chronic care, and when distances of equal length affect access very differently because of the characteristics of particular patient populations, transportation systems, and so forth.

Wilson and Blower seem unwilling to accept the notion that, in the furtherance of a rational strategy to achieve equity, some health authorities might decide, for example, to allocate a disproportionate share of ARVs to traditionally disadvantaged populations. Wilson and Blower's model could still be useful in allocating resources among the centers chosen (or established) to reach the target population, but the calculation would have to take account of more information about the centers and the population, lest assumptions about catchment areas produce a formal equality that does not translate into actual equality in access, much less into equitable access in light of all relevant factors.

Plainly, we share Wilson and Blower's aim of optimizing countries' responses to the tragedy of treatable, but untreated, HIV/AIDS. Any tools that are useful to that

end are welcome. But besides using models to distribute ARVs in a way that optimizes spatial equality, governments that want to achieve equity will need also to overcome nongeographic barriers to accessing treatment. These include ignorance, stigma, discrimination, and outright criminalization of vulnerable groups, as well as fees at point of service that are prohibitive for the poor. All of these are given attention within the context of the "3 by 5" program of the World Health Organization and the United Nations Joint Programme on HIV/AIDS, including in the guidance document on equitable access to ARV treatment cited in our commentary [4]. ■

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Citation: Capron AM, Reis A (2005) Authors' reply. *PLoS Med* 2(6): e186.

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Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020186

The Debate over Placebo-Controlled Trials

Franklin Miller

Turner and Tramèr provide a cogent argument in favor of the ethical use of placebo controls despite "proven effective treatment" [1]. However, they are wide of the mark citing the APPROVE trial in support of their position. Because there is no established treatment to prevent adenomatous polyps, few commentators would have any objections to the use of placebo controls in this study. Nevertheless, they are right to suggest that it would have been desirable to have included a placebo control in the VIGOR study to provide a more rigorous assessment of safety. Whether, all things considered, a placebo control would have been ethical in this study of treatment for rheumatoid arthritis is debatable.

Another issue not discussed in this *PLoS Medicine* Debate is the value of placebo controls in early "proof of concept" efficacy trials, despite the existence of established treatment. The efficiency of seeking a rigorous efficacy signal before moving on to larger-scale trials (and exposing as few subjects as possible to drugs that might not work or turn out to be toxic) is a valid ethical reason for using placebo controls, provided subjects are not exposed to undue risks of harm from withholding established treatment [2]. ■

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Citation: Miller F (2005) The debate over placebo-controlled trials. *PLoS Med* 2(6): e157.

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Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020157

Authors' Reply

We appreciate Dr. Miller's contribution to this debate [1]. Whether one uses his phrase "established treatment" or "proven therapy," we urge caution in using such a litmus test to decide whether the use of placebo is or is not acceptable. Such terms beg to be defined carefully. Should nonsteroidal anti-inflammatory drugs be considered "proven" for arthritis, despite their problems with assay sensitivity [2,3]? Dr. Miller states that there is no established treatment for adenomatous polyps. However, there is evidence from epidemiological studies and clinical trials supporting the use of aspirin and other nonsteroidal anti-inflammatory drugs for this condition [4–10]. Armed with such evidence—whether it qualifies aspirin as "proven therapy" is open to subjective interpretation—many placebo opponents, we maintain, would argue for an active-controlled design as a more ethical alternative to the placebo-controlled design actually used in APPROVe [11].

Dr. Miller focuses on the question of defending the use of placebo in the APPROVe study. This focus reflects the prevailing bias, which is to choose when it is acceptable to use placebo rather than to choose when it is acceptable to omit placebo. This bias is evident in the current version of the Declaration of Helsinki, with wording such as, "Extreme care must be taken in making use of placebo-controlled trials." Thus, the use of placebo is typically presumed "guilty until proven innocent," while active-controlled designs are presumed "innocent until proven guilty." The declaration is silent on the possibility that omitting placebo can lead to problems, too, as we have now witnessed with Vioxx.

So perhaps the more important question should be whether it was defensible to exclude placebo in the VIGOR study. Dr. Miller acknowledges that placebo would have provided a better assessment of the safety signal in the VIGOR study. Indeed, because placebo was not used, the authors were able to plausibly conclude that the difference between the two groups was due to naproxen causing benefit rather than to Vioxx causing harm [12]. (The plausibility of this conclusion has since been questioned [13,14].) This misleading safety signal only delayed the withdrawal of Vioxx. Its design was superficially ethical, but science was not advanced, and the public health was ill-served.

One might protest that these comments are made with the benefit of hindsight. It is true that the medical community

at large did not become aware of this safety issue until September 2004, when the results of the placebo-controlled APPROVe study were made public and Vioxx was withdrawn. However, according to David Graham's testimony to the United States Senate [15] and a report on internal Merck documents [16], there was good reason for concern about a possible safety signal before 1999, when Vioxx was approved and recruitment for VIGOR began [15].

If the VIGOR study had included a placebo arm, the truth about Vioxx could have been learned in February 2001 instead of September 2004 [14]. That is over 180 weeks during which the now infamous "two to four jumbo jetliners" were allowed to continue "dropping from the sky every week" [15]. Using the midpoints of Graham's range estimates, this works out to 94,500 excess heart attacks and strokes, including 33,000 deaths, in the US alone.

The authors of the VIGOR study said, "We could not include a placebo group" [12]. Was the idea of including a placebo arm suggested but rejected as "unethical," even though rescue medication could have been used? Or did they take the path of least resistance in the interest of rapid institutional review board approval and ease of patient recruiting? Whatever the reason, the decision to omit placebo led to ambiguity and inaction.

In clinical trials, whether one looks at efficacy (please see our opening argument in this debate [17]) or safety, omitting placebo often muddies the scientific waters and places the public health at increased risk. Good science and good ethics cannot be divorced from one another. We believe these considerations should factor into discussions on the ethics of clinical trial design. Before we experience another Vioxx, we hope that a future version of the Declaration of Helsinki will add, "Extreme care must be taken when omitting placebo." ■

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Citation: Turner E, Tramèr M (2005) Authors' reply. *PLoS Med* 2(6): e187.

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Competing Interests: EHT is on the speaker's bureau of Eli Lilly, AstraZeneca, and Bristol-Myers Squibb. He has provided outside consulting to Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Sepracor. He has also received funding for clinical drug trials, which can be spent only for research purposes and which has no effect on his income, from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, and DOV Pharmaceuticals. MRT has been a scientific consultant to Pfizer, Merck, Janssen-Cilag, and Sintetica. He has also received lecture fees from various pharmaceutical companies.

DOI: 10.1371/journal.pmed.0020187

Call for Biohistory Guidelines

Jordan Paradise

I am writing in response to an essay published in the most recent issue of *PLoS Medicine* by Deborah Hayden, entitled "Alas, Poor Yorick: Digging Up the Dead to Make Medical Diagnoses" [1]. As a co-author of the *Science* piece with Lori B. Andrews that Hayden references, I am troubled by her comment on our article. Nowhere in that article, "Ethics. Constructing Ethical Guidelines for Biohistory" [2], do we suggest that genetic testing be done on deceased individuals for historically significant questions. In fact, we specifically highlight some of the ethical, legal, social, and scientific issues that such testing raises and recommend that guidelines be developed in order to monitor current research that is being undertaken in this area. The article does not advocate biohistorical research. This distinction is very important and one that is quite evident upon a careful reading of our article. ■

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Citation: Paradise J (2005) Call for biohistory guidelines. *PLoS Med* 2(6): e192.

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Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020192

Author's Reply

The excellent article by Jordan Paradise, Lori B. Andrews, and colleagues, "Ethics. Constructing Ethical Guidelines for Biohistory" [1], neither advocates nor argues against biohistorical research; instead, it points out that such investigations are currently taking place without guidelines—ethical, scientific, moral, or religious. The question remains: if such guidelines were to be established, what individuals, institutions, governments, medical examiners, family members, or intrepid biographers are to be given permission? Who is to decide what is "historically significant"? Not to mention the meta-question: who is to decide who is to decide? I apologize to the authors if my brief comments [2] implied that they took a position on this issue. ■

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Citation: Hayden D (2005) Author's reply. *PLoS Med* 2(6): e191.

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Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020191