What are the effects of the fifth revision of the Declaration of Helsinki?

The World Medical Association's fifth revision of the Declaration of Helsinki strives to strike a balance between ensuring high ethical standards and retaining sufficient sensitivity to local circumstances, especially in developing world research, to avoid thwarting research with bureaucracy. Has the balance been achieved? We asked researchers working in the developing world, the developed world, and the pharmaceutical industry, as well as a patient representative, to comment.

Fair partnerships support ethical research

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The World Medical Association describes the Declaration of Helsinki as a statement of ethical principles to guide physicians and other participants in medical research involving human subjects, including identifiable human tissue or data.[1] When producing the fifth revision, representatives of the 71 affiliated medical associations were especially concerned that research in developing settings—and particularly clinical trials—meet the highest ethical standards of conduct. However, despite the increasingly inclusive aspirations of the revised declaration, some of the absolute and exclusionary language could unintentionally endanger research in developing countries.

Use of placebo controlled trials

One of the fundamental changes to the declaration is clause 29. This states that new treatments should be tested against best current treatment rather than placebo (box). The clause was formulated in response to sustained criticism of field trials in developing countries that tested short course therapies aimed at preventing vertical transmission of HIV using placebo controls.[2–4] It implies that local circumstances—sociopolitical, financial, infrastructural, cultural—can never justify failure to use the best known drugs or technologies in the control arm. Its intention is clear:

- To ensure that the interests of trial subjects, no matter where they live, are fully recognised
- To prevent the exploitation of vulnerable communities by profit driven pharmaceutical companies testing drugs for the developed world markets, and
- To ensure that medical researchers worldwide apply consistent ethical standards to their research designs irrespective of the local setting.

However, in seeking an absolute yardstick, the latest Helsinki revision may harm the interests it intends to protect. Health and public sector systems in much of the world—particularly sub-Saharan Africa—are extraordinarily weak; the human capacity to staff and manage these systems is seriously inadequate.[5] Overlapping epidemics of infectious and chronic disease, exacerbated by the burden of HIV and AIDS,[6] are imposing unparalleled demands on local services and social resources. Thus, clause 29 may impose demands on local and national health systems that, without massive additional investments, simply cannot be met.

Clause 29 of the Declaration of Helsinki

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

In consequence, the important and legitimate expectation that "medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" (clause 19) may be unintentionally invalidated because the requirements for sustainable provision of new treatments exceed the capability to deliver. Similarly, the intention that, at the end of the study, every participant should have access to the best prophylactic, diagnostic, and therapeutic methods identified by the study (clause 30) would be difficult for many local health systems to fulfil.

The HIV and AIDS pandemic, and the desire to short circuit its accelerating momentum, has undoubtedly driven the debate around the Helsinki revision. Had such ethical imperatives been applied previously, we might not have conducted the research that resulted in oral rehydration therapy, micronutrient supplementation, certain low cost surgical procedures,[2] and insecticide impregnated bed nets.

The best current methods for transplant surgery or against organ rejection cannot be separated from the research and healthcare settings that make such practices possible. With respect to HIV and AIDS, certain realities need to be faced. For example, in much of rural Africa, pregnant women present late to antenatal care and may be anaemic and undernourished. In addition, health services, whether public, private, or some mix of these, may be unaffordable or inaccessible.[7]

I am not arguing that ethical standards should be compromised or that there is a case for moral relativism. I am simply endorsing the view that "considerations of context are required aspects of moral reasoning in the application of universal principles to specific situations."[8] In considering context, and to avoid an excessive reliance on our own preferences or expectations, it is essential to seek mutually respectful, equal partnerships with those with whom we intend to collaborate.

Whether and how to relax the restriction on placebo controls remains on the World Medical Association's agenda. In September 2001, the association's council met with representatives of several stakeholders in medical research to discuss when it is ethical to use placebo controlled trials.[9] Although no change to the declaration can be considered before the next assembly in 2002, subtle refinements to clause 29 could be proposed.

Other revisions

Although most attention has focused on the crucial clauses affecting conduct of clinical trials, other modifications to the text of the declaration also deserve mention. Changes to section A, the introduction, extend the focus and scope of the declaration. The revised declaration includes scientists as well as doctors, if only to a limited extent; expresses concerns about the costs and availability of prophylactic, diagnostic, and therapeutic methods; introduces the language of measurement science (risks) and human rights; and recognises the needs of economically and medically disadvantaged people and other vulnerable populations—not only individuals.

SEAN SPRAGUE/PANOS PICTURES

Demands on health systems in developing countries will make it difficult to fulfil all the aspirations of the Helsinki declaration

Section B substantially strengthens the oversight role of a fully independent ethical review committee (clause 13) but does not recognise any special responsibility of the host country for ethical review. Although ethical review processes in many, particularly developing, countries are weak or inadequate, this does not justify such an omission. In many Asian and Latin American settings, and African settings such as South Africa or Uganda, ethical review procedures are increasingly integral to national research processes and need recognition and reinforcement.

Clause 15 holds that all medical research on human subjects should be conducted under the supervision of a clinically competent medical person. Given that the definition of such research now includes studies using any identifiable data (often data on populations), this line of reasoning runs counter to a broader health research agenda, which is often multidisciplinary and may be led by epidemiologists, economists, or other social scientists rather than exclusively by physicians.

Helsinki, Bangkok, and beyond

Worldwide, awareness is growing that the evidence base for health policy and practice in developing countries is unacceptably thin. Nevertheless, the global research effort overwhelmingly targets the world's healthiest populations.[10] In October 2000 (at almost the same time as the World Medical Association assembly that finalised the fifth revision of the Helsinki declaration), health research leaders from over 100 countries convened in Bangkok, Thailand, to discuss concerns about the uneven progress since the report *Health Research: Essential Link to Equity in Development* was presented to a Karolinska Nobel conference in 1990.[11] Participants aimed to strengthen the voice of scientists in developing countries.

The unanimously adopted Bangkok declaration emphasises the need for an effective health research system that will require "coherent and coordinated health research strategies and actions that are based on mutually beneficial partnerships between and within countries."[12] A central challenge will be the development of sustainable health research systems at country level.

If medical research in developing countries is to meet the high ideals of the Helsinki 2000 revision, long term individual and institutional scientific partnerships will need to be formed and sustained (box). The Bangkok action plan calls for a "universal code of good practice [which] should not only cover traditional bioethics … but should extend to the ethics of partnership and practice."[12] Clearly, this refers to the importance of well balanced research collaborations that seek to ensure a fair flow of benefits (and obligations) among participating scientists. These include (both procedurally and substantively) fair allocations of research roles, infrastructure investments, and authorship and related credits, along with meaningful contributions to developing capacity among local researchers, health services, and communities.

Extensive regional consultations in Africa, Asia, the Caribbean, eastern Mediterranean, Latin America, and central and eastern Europe informed conference

Potential benefits of balanced research collaborations with developing countries

Strengthening of local ethical review processes
Providing opportunities to national researchers
Challenges to unfair research practices
Contributions to development of local health systems

deliberations in Bangkok.[13] To a striking degree, these spoke of developing country researchers' sense of exclusion or alienation from international research processes. The challenge of fairness in collaborative research relationships should not be underestimated. Given a reality where some participants enjoy "the overwhelming power of assertion,"[14] local research leaders will need to strengthen their understanding of the research environment, express clearly their scientific and institutional needs, and recognise the need to negotiate for these.

Nevertheless, securing well balanced research collaborations in the service of poor and disadvantaged communities will provide the social and scientific capital to effectively navigate what are at times ethically murky waters. Successful scientific partnerships will, in time, come to influence broader decisions about research priorities and research investments.

Helsinki: the next revision?

The process of revising the Helsinki declaration has had positive effects on other ethical codes.[15] Discussions about future revisions should take account of the views of the leaders of health research who met in Bangkok. The process of finding common ground between the two groups will undoubtedly help meet their complementary goals of strengthening the ethical conduct of research in developing countries and contributing to effective health research systems.

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Gains and losses for rights of consumer and research participants

Hilda Bastian

The latest revision to the Declaration of Helsinki was precipitated by concern about Northern researchers exploiting populations in poorer countries.[1] It is too soon for consumer groups to have broadly based responses to the revised declaration. Nevertheless, some gains and losses from the previous version can be identified. Most of the gains are straightforward and clear (box), so I have focused on some weaknesses of the declaration.

Protectionism versus ensuring people's rights

The declaration has a predominantly protectionist ethos towards the community and individuals approached to participate in research. This is perhaps inevitable, given that the original declaration was developed in response to research atrocities identified in the 1947 Nuremberg trial. The right of people to safety is the first of the internationally recognised consumer rights.[2] Ensuring safety was critical last century, and it remains just as vital now. However, it is only one of our rights, and considering research in a broader rights context highlights some of the major limitations inherent in this (and other) codes.

The declaration has aimed to ensure people's right to autonomy, and through its various revisions it has started to move closer to ensuring a broader range of rights. However, there has been no systematic focus on the breadth of community and individual rights. Thus, the declaration still falls short in many areas, such as the right to choose, the right to be heard (and the corollary, to participate in important decisions), and the right to redress when harmed. Even the right to be informed is not fully articulated. The right to information is acknowledged only before entering a study. Researchers are not expected to inform participants of the study's results.

The predominantly individualist approach of the code also means that issues relating to communities' rights fail to emerge. In addition, the declaration omits issues related to individuals that cannot be dealt with

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Gains for consumer rights

- Even current "best proven" treatments should be challenged by research
- Research should be done only if it can benefit the population being researched
- New duty to disclose (and publish) funding and potential conflicts of interest
- Obligation to ensure people have understood the information provided to them
- Obligation for informed consent before using unproved treatments outside research (with duty to keep proper records and undertake research)
- Duty to safeguard confidentiality of patients' information
- Ethics committee should be independent of any undue influence and have the right to monitor research
- After the study is finished, participants should have access to the best treatment the study identifies
- Design of all studies to be publicly available, and ethical obligation to make positive and negative results public

Changes resulting in gains and losses

- Potential for research to be stopped before risks of treatments clear (but beneficial treatments potentially available sooner)
- Right of all groups in a study to receive best proved treatment, with limitation on the use of placebos (but potentially better comparative information on treatments)

by looking at research, only on a case by case basis. For example, there is no ceiling on how many times a person can be invited to participate in research during an episode of care or any consideration of the effect repeated invitations might have.[3] Ensuring people's right to choose would mean not just giving them the right to say "yes" or "no" to a particular study but providing access to knowledge of all research in which they might want to participate.

Access to research

Access to research is one of the missing pieces in the declaration's approach. Although it is important to protect communities from exploitation, it is also essential to consider the other side of the coin. The guidelines by the Council for International Organizations of Medical Sciences, an offshoot of the declaration, at least acknowledge the need for "equitable distribution of burdens and benefits," albeit with a limited approach to this concept.[4]

The reality is that participation in trials has effectively become a way to access new treatments, and in poor communities it is often the only way to get any formal health care.[5,6] If, as the Helsinki declaration hopes, ongoing treatment after a study becomes part of the package, the stakes for access rise considerably—as does the coercive potential. The effect that this would have on a community's ability to determine an equitable distribution of healthcare resources also needs considering.

Some researchers are arguing that there is strong evidence that people treated within randomised controlled trials (regardless of being in a treatment or control arm) fare better than those treated outside trials.[7] If this proves to be true, it would challenge the concern about special risks of research that forms the basis of the declaration.

"Vulnerable" groups

One of the justifications for the protectionist and exclusionary approach has been concern for so called vulnerable populations. Increasingly, populations that are designated by others as "vulnerable" are arguing on their own behalf for a philosophy of inclusion rather than exceptionalism and discriminatory exclusion.[8] Exclusion from health research can result in a lack of relevant evidence needed to make basic healthcare decisions.[9–11] Agencies such as the National Institutes of Health in the United States are taking action to redress this,[10,11] but the declaration still takes the "exclude unless unavoidable" approach. Perhaps the danger of exploitation remains greater than the dangers of exclusion or discrimination, but the World Medical Association has done nothing to show that this is so.

Meanwhile, the declaration has taken a step backwards for people who are legally "incompetent" to make their own decisions (including those under 18 years old) but who are in fact capable of doing so. The declaration downgrades the previous requirement for consent from people in this category to "assent" (with consent reserved only for the legally authorised representative). In Australia and many other countries, national guidelines ensure that whenever anyone is capable of making his or her own decisions, full consent must be sought and respected.[12]

This issue is one of many where adhering solely to the Declaration of Helsinki rather than a community's codes would lower standards. Many countries, in both the South and the North, seek to meet their communities' legitimate expectations in ways that surpass what the World Medical Association has constructed. However, the declaration requires only that researchers "be aware of" other ethical and legal requirements. A new provision claims that no law or ethical or regulatory requirement should be allowed to reduce or eliminate the protections it sets out. But there is no statement that the declaration should not be used by researchers to sidestep better or more onerous provisions.

Will (or should) the declaration still have so much authority?

The World Medical Association has changed the designation of the declaration, from "recommendations" for doctors, to "ethical principles" for everybody involved in research. This extension of medical dominance in ethics reflects enormous presumption by the association.[13] This presumption is probably not justified.

When it was first created, and for many years subsequently, the declaration was a vital pioneer in setting and raising ethical standards in research. It may still be in some ways and in some areas. Nevertheless, the World Medical Association is a political organisation, representing some of the "doers" of research only (and with no mandate to speak on behalf of the "researched"). The organisation has been described as "still struggling to gain credibility and clout."[14] This struggle was not helped by the difficulties it had in the 1990s trying to remove its president (a former SS officer implicated in a human rights transgression).[15]

The declaration, and the association's claimed stewardship of ethics in the 21st century, has critical

underlying weakness. It is not derived from a process including serious engagement with the people it seeks to protect; there is no accountability to anyone other than the medical profession (and perhaps the ethics industry); and there is no apparent evidence base or solidly articulated rationale for much of what is contained in it.

Many (if not most) of the research ethics committees that the Declaration of Helsinki originally led into existence now have some kind of community representation,[16] albeit often token.[17] Many researchers and research ethics bodies are seeking to work with the community rather than assuming some kind of paternalistic or sovereign position over it.[18] Perhaps it is simply too much to hope for—that an organisation that does not share decision making with the community should be able to lead ethical development in a more democratised world. Yet, a meaningful role for the community in determining what is essential to enhance people's health and their ability to exercise their rights is long overdue, both at global and local level.

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Research will be impeded

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Ethical considerations are fundamental to both the practice of medicine and medical research, and the promulgation of any ethical guidelines therefore needs serious thought. Unfortunately, the guidelines recently issued by the World Medical Association seem, in some respects, to have been laid down without proper appraisal of the nature of the activities to which they are intended to apply.

Diversity of medical research

Medical research is not a single entity but involves many different types of inquiry. At least five types can be distinguished (box). Research in which patients are required to take drugs or have invasive procedures (types 1 and 2 in the box) might expose participants to some hazard, even if only tiny. It is to these two types of research that most of the Declaration of Helsinki's principles may properly be thought to apply. Even here, however, some of the principles show a lack of understanding of what their effects would be if rigidly applied, notably in controlled trials.

Other types of research, however, expose subjects to no hazard, apart from the rare instances in which asking questions might be thought to cause psychological distress or, importantly, detriment might occur if the identity of individuals did not remain confidential. Surely the time is past when anyone continues to think that possession of an individual's hair, blood, or faeces would enable harm to be caused to that individual, outside the fictional world of Harry Potter.[1] It is consequently difficult to take seriously a whole series of principles that, according to the declaration, apply without distinction to all types of medical research involving human subjects, including research on identifiable human material or identifiable data.[2]

Types of medical research

1 Research carried out solely in the hope of increasing scientific knowledge in which participants are required to take drugs or have some clinically invasive procedure

2 Research into the relative merits of different treatments for a disease or condition

3 Research using biological material that has been obtained from an individual for other purposes

4 Research that requires participants only to answer questions, have simple procedures, or have the characteristics of their environment recorded

5 Research making use of existing medical records

Effect on research

Strict application of the declaration's principles would make a wide range of clinical, biological, and epidemiological research impracticable or invalid. An

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example is the investigation I did with Court Brown to find out the relation between the dose of ionising radiation to which an individual was exposed and his or her subsequent risk of cancer. We were asked to conduct the research shortly after the explosion of the first hydrogen bomb in the Pacific, which caused radioactive fallout throughout the world. We answered the question by collecting information from the records of patients given radiotherapy for ankylosing spondylitis throughout Britain over the previous 20 years and matching their names against the records of people dying from leukaemia, then a fatal condition.[3] We could not have done the study if we had had to locate and seek the consent of the 14 000 patients before doing the analysis.

Another more recent example is Goldacre et al's case-control study comparing admission rates for breast cancer and other diseases in women who had been admitted to hospital for either induced or spontaneous abortions by using data from the Oxford record linkage study.[4] They found that neither type of abortion increased the risk of breast cancer. Again, the results could not have been obtained by studies involving personal inquiry because of the potential bias in the recall of such emotional events.

If carried out to the letter, the principles of the declaration would also affect the conduct of controlled trials—particularly in developing countries. For example, it would be impossible to test a new treatment that was economically affordable when potentially better but unaffordable treatments were known to be in use elsewhere (clause 29).

Ethics and data monitoring committees

The World Medical Association does not seem to recognise the existence of data monitoring committees and the difference between their function and that of the local ethics committees (clause 13). Ethics committees initially approve a trial's conduct. Data monitoring committees, on the other hand, are appointed specifically for each trial, and the members are chosen to include some with special knowledge of the problems likely to arise. Asking researchers to provide interim information of the trial's results to any group other than the trial's data monitoring committee is a recipe for producing inconclusive results.

Finally, I am appalled by the distress that fully informed consent may sometimes cause in the absence of the escape clause that was present in the 1964 declaration.[5] Telling acutely ill patients with a possibly fatal disease precisely what their chances of survival are contravenes the first principle of the old Hippocratic oath—not to cause the patient avoidable harm. There was, and continues to be, much to be said for enunciating only a few broad principles and allowing the details to be decided in each case in the light of the circumstances and the physician's aim to do good.

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Some clauses will hinder development of new drugs and vaccines

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The Declaration of Helsinki has provided widely accepted ethical principles for medical research involving human subjects since its adoption in 1964. All recent Merck protocols for such research include the 1996 declaration.[1] Independent institutional review boards or ethical review committees review and approve all Merck trials in accordance with ethical guidelines and applicable national and international regulations. The 2000 revisions to the declaration,[2] however, include several provisions that we believe do not provide better protection for participants in clinical trials and could inadvertently hamper the development of safe and effective new drugs and vaccines.

We, along with other research organisations, regulatory agencies, and advisory bodies,[3 4] were especially concerned about the wording of clause 29, regarding use of placebo controls in clinical trials. The note of clarification recently published by the World Medical Association[5] addresses these concerns by acknowledging that a placebo controlled trial may be ethically acceptable under certain well defined circumstances. We look forward to the official adoption of revised wording at the World Medical Association general assembly next year.

Other problems

Nevertheless, several other sections of the 2000 declaration still need clarification. Two of these are clause 30, concerning treatment after the trial, and clause 27, concerning publication of trial results.

The new declaration (clause 19) appropriately recognises that "medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." Clause 30 extends this by requiring that "at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."

We agree with the principle of providing participants with access to effective therapy for some time after the conclusion of the trial. However, the wording of clause 30 raises concerns. Firstly, none of the meth-

ods used in the study may be found to be suitable. Secondly, a single study can rarely identify "best" treatment. This is especially true for early stage trials, including proof of concept studies and dose ranging studies. Thirdly, a new drug or device may not be approved until several years after the end of a trial. Consequently, providing as yet unapproved treatment to trial participants on completion of the study may conflict with local regulations. Finally, an offer to provide treatment that is otherwise unavailable on completion of the trial might be considered an undue inducement to potential participants.

Improvements in medical infrastructure require collaborative efforts between public and private partners; mandating that sponsors of studies provide treatment is not, by itself, the answer to this complex issue. The best way to provide treatment after a trial will vary with local conditions and infrastructure and should reflect input from local healthcare providers.

We agree that "negative as well as positive results should be published or otherwise publicly available" for studies designed to test hypotheses (clause 27). Merck has and will continue to publish results of hypothesis testing clinical trials in the peer reviewed medical literature, regardless of the results.[6 7] However, we do not always publish early studies, including phase 1 and 2a trials that are typically exploratory pilot studies aimed at generating hypotheses rather than testing them. This is an important distinction. Publication of such pilot studies would disclose early findings that could be used by competitors.

Human subjects who participate in medical research can be protected by ensuring that clinical research protocols have a scientifically sound design. With appropriate modification, the revised Helsinki declaration should help to do this. We are encouraged by the council's clarification of clause 29 and its appointment of a panel of advisors to help with the continuing review of the declaration.[5]

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Correction

Understanding the toll of premature death among men in eastern Europe

In redrawing figure 1 in this article by Martin McKee and Vladimir Shkolnikov (3 November, pp 1051-5) we unfortunately mislabelled the y axis, and the error was not noticed before publication. This led to male life expectancy in Europe being represented at a severely reduced level. The range on the y axis should start at 60 [not zero] and should therefore read "60, 65, 70, 75, 80" years.

A memorable patient

The importance of keeping contemporaneous records

Oliver was born the day after my daughter was, and I remember his mother was on the labour ward when my wife was in labour. She unfortunately had prolonged rupture of membranes that led to a stormy neonatal period with sepsis, jaundice, and feeding problems. He has had an uneventful childhood apart from an assortment of coughs and colds.

Recently, Oliver was seen by one of our nurses with a tick on his eyelid, and this was easily removed after the application of a liberal coat of petroleum jelly overnight.

Three weeks later he developed conjunctivitis, for which I prescribed chloramphenicol drops. He subsequently saw various doctors in the practice, the notes are well written and thorough, and in retrospect we should have made the diagnosis sooner as all the clues were there.

Four days after the conjunctivitis, he developed a rash on his cheek, although the conjunctivitis was better. The entry reads "?erythema marginatum but heart sounds ok, no organomegally, probable viral illness." However, there was an annotation to the entry by the nurse relating to the tick bite suggesting the tick had been present for over 24 hours.

Several days later, he became unwell with a fever. The facial rash had resolved, but examination by another doctor showed a high temperature, enlarged tonsils, and clear urine on multistix.

After three weeks he was still unwell, lacking energy and anorectic. He was seen by the original doctor, and the penny dropped (with a clang). The rash on Oliver's cheek was erythema chronicum migrans (ECM). This usually arises centrifugally from a tick bite, but secondary annular rashes can arise in the vicinity, as in this case. He was given high dose penicillin, and serology for *Borrelia burgdorferi* proved positive after a further week, confirming the diagnosis of Lyme disease.

Fortunately Oliver developed no neurological or rheumatological sequelae and made a full and uneventful recovery, but he had given his parents considerable worry during his illness. His mother subsequently told me that she thought he had leukaemia.

I have always been an advocate of thorough contemporaneous records, which are then a useful management tool for all members of a primary healthcare team. Increasingly, we are working as an extended team, and patients may see the nurse practitioner, health visitor, physiotherapist, or doctor. Difficulty with access may make continuity of care problematic, and it behoves all of us to read the entries of our fellow professionals as an aid to accurate diagnosis.

I am always suspicious when a patient presents for the third time with a problem that has not resolved and am always keen to consider physical rather than psychological causes in the first instance.

Critical event analysis assesses whether important clues have been missed in the presentation of serious or unusual diseases, and it has highlighted some shortcomings in this case from which we have all learnt a valuable lesson.

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