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Comparison of ethical issues in Indian and New Zealand prospective studies of cervical pre-cancer

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Abstract

The aim was to compare the ethics of historical Indian and New Zealand prospective studies of cervical pre-cancer in terms of: scientific justification, potential harms and benefits to subjects, informed consent procedures, monitoring and stopping, and exploitation.

The New Zealand study had poorer scientific justification, greater harm to subjects, absence of informed consent, and greater exploitation.

Reasons proposed for on-going criticism of the Indian study are: semantic confusion, lack of consistent detail about informed consent procedures, and failure of a professional obligation to provide on-going medical care. Such criticisms might have been set on a firmer basis, or rejected, if there had been a public judicial inquiry, as happened in New Zealand. Current disagreement about the ethics of randomised trials of cervical screening in India might be resolved through a public inquiry.

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Introduction

There are striking similarities, as well as important differences, between two Indian and New Zealand prospective studies of cervical pre-cancer that gained public attention for alleged unethical practices. The allegations centred on dangers to women subjects, whose pre-cancer was followed but not treated, and inadequacies of informed consent. For the Indian study, it has also been alleged that there were substantial delays after referral for treatment when the disease had progressed.

These are historical studies: New Zealand's "Unfortunate experiment" on women with carcinoma *in situ* (CIS) of the cervix started in the 1960s and came to public attention in the 1980s (1); the Indian "observational study" of cervical dysplasia started in the 1970s and came to public attention in the 1990s (2). Both were investigated by a judge: in New Zealand a committee of inquiry led by Judge Silvia Cartwright was established by the government in 1987; in India a seven member inquiry committee headed by a retired judge was set up in 1997(2).

Though both studies were investigated independently, more facts about the New Zealand study are known - because the inquiry was held in public and a detailed report published - whereas the Indian inquiry was held in private and no report is available, though the inquiry exonerated the researchers (personal communication). Moreover, a "case study", based on the Indian study, published by the World Health Organisation

(WHO) in the *Casebook on ethical issues in international health research* (3), provides some different information from that in the main published reports of the study (4, 5). With these caveats, there is still enough information on the aims and conduct of both studies to compare the central ethical issues.

Although the studies are historical, in what follows I do not rely on when particular ethical codes were promulgated. As Brookes and I have argued elsewhere (6), too much attention to the existence and authority of codes can be used to imply that everything done before such codes is immune from criticism. Where time matters is in considering empirical questions. Knowledge of the natural history of cervical cancer and of the effectiveness of cervical screening using the Pap smear has accumulated over time and this affects ethical judgements about known potential for harm or benefit. Moreover, cervical screening programmes have been introduced at different times in different places; this context is also relevant.

In what follows I first describe the timing of the implementation of cervical screening and of accumulating knowledge of the natural history of dysplasia and CIS. This is followed by an outline of the two studies in terms of: the aims and designs, scientific justification, potential harms and benefits to subjects, informed consent procedures, monitoring and stopping, and exploitation. Lastly, I discuss the overall comparison and why the Indian study might have come in for such strenuous criticism when the ethical breaches, at least in comparison with the New Zealand study, appear to have been relatively minor.

Background on cervical cancer screening and pre-cancer

Cervical screening, using the Pap smear, started in the 1940s and 50s in industrialised countries. The rationale for such screening was that it would detect a pre-cancerous condition, carcinoma in situ (CIS), in which abnormal cells, like cancer, are present but are confined to the surface epithelium and have not invaded the underlying tissue – the hallmark of cancer. Detecting and treating CIS should, hence, reduce the incidence of and mortality from cervical cancer. By the 1960s, there was evidence that CIS, if left untreated, progressed to invasive cancer in a proportion of cases and that cervical screening was probably effective (7), though there was no strong evidence until the 1980s (8). Cervical screening was available in New Zealand from the 1950s and in the 1960s there were campaigns to increase screening uptake (9). Since the 1980s, national cytology screening programmes have been introduced in many countries, though not in India. Cervical cancer remains the second most common cancer among women in India, where scaling up of other methods of cervical screening is underway (10).

When screening is introduced into a country, the expectation (and ethical obligation) is that the people with screen-detected disease will be treated according to some agreed policy (7). Nevertheless, there may still be uncertainty about which screen-detected conditions should be treated. Cervical

cytology screening in the 1950s and 60s was intended to detect CIS, but cervical screening also detected more severe abnormalities – early invasive carcinoma, and less severe abnormalities – dysplasia. Clearly invasive cancer should be treated, but there has been less certainty about the balance of benefit and harm from treating dysplasia. An authoritative trial of following dysplasia without treatment was published in 1969 (11). Richart and Barron gave their rationale for the study: “There would appear to be general agreement that carcinoma in situ represents a preinvasive form of cervical cancer but the precise significance of cervical dysplasia has been a source of controversy.” They reported earlier studies in which around 50% of dysplasia cases regressed; if regression were common, then treatment for this group might constitute unnecessary over-treatment. In fact their findings supported the theory that different grades of dysplasia lay on a continuum towards CIS and they recommended that all grades should be treated. But subsequent studies have continued to find variable results. A meta-analysis, published in 1998, of studies of untreated dysplasia found that 21% of low-grade lesions progressed to high-grade in 24 months; while regression to normal occurred in 47% of low-grade and 35% of high-grade lesions (12). Five follow-up studies of untreated low-grade lesions were published after the Indian study, and one of high-grade lesions.

The terminology used to describe Pap smear abnormalities has changed over the years, reflecting the difficulty in reliably distinguishing different grades of dysplasia, as well as better understanding of changes due to human papilloma virus (HPV) infection – which is the necessary cause of cervical cancer. The cervical intraepithelial neoplasia (CIN) terminology, in which high grade dysplasia was combined with CIS as CIN3, was first used in the 1970s (13). More recently, the squamous intraepithelial lesion (SIL) terminology incorporates CIN2 and CIN3 in high grade SIL (HGSIL) and CIN1 is LGSIL (14). By the 1990s, there was agreement that high-grade lesions should be treated but, for low-grade lesions, either immediate treatment or follow-up and treatment if the abnormality progresses were both accepted options (15).

Comparison of ethical issues in the two studies

A comparison of the studies' aims and designs

The aim of the New Zealand study was to investigate the natural history of CIS of the cervix, in an attempt to prove that CIS was not a precancerous condition (1). The investigator, gynaecologist Herbert Green, wrote that he was attempting to “follow indefinitely patients with diagnosed but untreated disease” (16). It entailed observation, but should not be classified as an observational study. It was an experiment, or intervention study, because the conditions were under the control of the investigator. Green received permission from the hospital medical committee to undertake an intervention that entailed *withholding* conventional treatment (cone biopsy with follow-up to check disease had been eradicated) from women with CIS. Women with a histological diagnosis of CIS, without complete removal of the lesion, were followed up to detect

whether the disease became invasive. Women with CIS of the vulva were also included, though not part of the approved study (17). The endpoint was clinically invasive cancer (women with microinvasive cancer were also not treated) (18). Women were not randomised to intervention and control groups, but there was an implicit comparison group of women who received conventional treatment at the hospital.

The aims of the Delhi study were to investigate the natural history of early cervical lesions (dysplasia), to identify factors that affected progression to CIS, and to identify risk factors for dysplasia (4). The endpoint was CIS. Although it has been described as an observational study, it is arguably best described as an intervention study. In this population in Delhi from which women attended gynaecological clinics at six hospitals, there had been no screening programme and none of the women had had a previous cervical smear (4). Hence setting up screening for a specific group, for research purposes, meant that the conditions of study were under the control of the investigators. In this case, the intervention was cytological screening and follow-up of those with dysplasia without treatment. It is not clear whether monitoring instead of treatment for women with mild and moderate dysplasia would have been a departure from normal care in the 1970s, even in countries with established screening programmes. For severe dysplasia, which became incorporated in CIN3, treatment would probably have been routine elsewhere by that time. There was a comparison group of women who were also screened, but had normal results. This control group was used only in the investigation of risk factors for dysplasia.

The key ethical questions about the designs of these studies are: first, whether they were scientifically sound and justified; and second, whether they were in the best interests of the women subjects themselves in terms of potential harms and benefits. Was it ethical to allow these studies to proceed in the ways they were designed?

According to Green, the New Zealand study was justified by a lack of evidence that CIS was a precursor of invasive cancer (16). But other experts at that time disagreed, citing direct and indirect evidence for progression (19). The weight of evidence suggests that it was not justified from the outset. Nevertheless, if we are open to challenges to conventional thinking, perhaps a trial of no treatment, with informed consent, monitoring, and plans for stopping if cancers were diagnosed, might conceivably have been justifiable. There was no proper protocol for the New Zealand study and no designated control group. However, the most serious scientific problem was that Green misrepresented the study findings – removing cases that developed invasive cancer – so his publications could not be relied on (1, 20).

In the New Zealand study, the women were at risk of two sorts of harm: that the original limited diagnostic biopsy had overlooked an already existing invasive cancer, and that women would develop invasive cancer because their CIS was left untreated. Though Green argued that these risks were negligible, the weight of expert opinion was against him. The

harms also included having to attend the hospital repeatedly over many years. The benefit in the short term was being spared surgery (adequate cone biopsy), though in the longer term many women underwent repeated biopsies to check for invasive cancer, with resulting morbidity (1, 21)

The Delhi study was justified, according to the authors, by a lack of knowledge about the behaviour of early pre-cancerous lesions and relevant risk factors for disease occurrence and progression. Such knowledge was required, they argued, specifically for developing countries, in order to develop programmes to prevent cervical cancer (4, 5). This was at a time when herpes simplex virus type-2 and then HPV were being considered as possible causes of cervical cancer. It is likely that information specific to a country is useful because risk factors differ in prevalence among countries. The study was undertaken by the Cytology Research Centre, Indian Council for Medical Research, so the results were able to be applied to the country itself. No questions have been raised about the accuracy of reporting of the results. The two main study reports have been widely cited.

In the Delhi study, the potential harms and benefits of inclusion were different from the New Zealand study, apart from both groups having to repeatedly attend the hospital for follow up. Women who, at the initial examination, had a diagnosis of CIS or invasive cancer were to be referred for treatment. The authors wrote: "For obvious ethical reasons, the end point of the study was carcinoma in situ, at which time appropriate treatment would be offered." (4) Similarly, women who developed CIS or early invasive cancer during follow-up were to be referred for treatment. This, in the context of no cervical screening outside the study, was a benefit, as no treatment would have been available otherwise until their condition produced symptoms of invasive cancer. Treatment for clinically invasive cancer is more radical and there remains a substantial risk of death.

For women with the milder grades of dysplasia, a proportion would have been expected to regress to normal during follow-up. Women with mild dysplasia whose lesions regressed would not have been harmed by being followed without treatment, though neither would they have benefited. It is unclear whether women who continued to show dysplasia at the end of the study were to be referred for treatment, as they would have remained at risk. For women diagnosed with severe dysplasia, there was evidence from Richart and Barron's study that 50% would progress to CIS in 12 months (11). As long as they were followed closely (the protocol was three monthly) and diagnosed with CIS, treatment at that stage would have been the same as for severe dysplasia, so no further harm would have resulted. The women ran a small risk of developing early invasive cancer (in Richart and Barron's study, 3 patients out of 557 developed invasive cancers). The WHO case study notes that women were referred to the nearest regional cancer centre, which had a very long waiting list; by the time some of these women were seen, the lesion had progressed to a higher level. Although it is still very likely the women in the study were

advantaged compared to the women outside, there remains a question about special obligations to research participants.

Comparison of informed consent procedures

For the New Zealand study, no consent was sought. Indeed only a few women suspected they were part of a research study (1). In publications arising from the study, Green made no mention of consent. This failure had serious consequences for the women: they were kept in the dark and did not know they remained at considerable risk of developing invasive cancer. Some women lost to follow-up presented eventually with late stage disease. For the Indian natural history study, explanations of the consent procedures appear in the published papers. In 1987, Luthra et al stated:

All women registered for long-term follow-up were informed about the objective and purpose of the study and also the cooperation that would be required of them. The individual registered as a dysplasia case was informed that she had a lesion that could either regress to normalcy or progress to higher grades of atypicality and was then given the option of either being followed or of being discharged from the study. Patients choosing the latter alternative (15%) were appropriately managed (4).

In the 1990 report, Murthy et al presented the details somewhat differently:

Dysplasia subjects and their husbands were contacted by a team of trained medical social workers and gynaecologists to educate them about the objectives of the study and to elicit their cooperation. All the subjects agreed to participate in the study (5).

Thus the written evidence shows that relevant information was given to participants and that consent was sought, though not in writing. It is hard to understand why the two accounts of consent differ, nor is it clear what "appropriately managed" means.

In the case study, puzzlingly, the details of consent depart from both accounts:

The researchers did not inform the women that their lesions might progress to cancer. Women were not made aware that treatment was available (3).

Did the writers of the WHO case study have access to other information that contradicted the published accounts, or were the details changed to make the study less identifiable? Or was there confusion about the definition of cancer? The authors of the papers emphasised that "for obvious ethical reasons" the end point at which treatment would be offered was CIS, not cancer.

Monitoring and stopping rules

The purpose of monitoring an intervention study is to identify harms (or benefits) while the study is in progress that might necessitate stopping the study early. Stopping rules are predetermined decisions about the level of harm or

benefit that requires stopping, taking into account statistical uncertainty and the frequency with which the data are examined.

The New Zealand study had no formal monitoring and no stopping rules (though the latter would have been uncommon at the time). The investigator, Green, monitored the study, though he misrepresented the results in his published papers by re-classifying cases that had developed invasive cancer as invasive at the outset and excluding them from his series (1). Nevertheless, the study was informally monitored by the colposcopist and cytologist (McIndoe) and the pathologist (McClean), who were concerned about the increasing numbers of invasive cancers among women in the study. They tried to reason with Green, and when that failed they complained to the Medical Superintendent of the hospital about the dangers to patients. That led to an internal inquiry which reported in 1975 but did not recommend stopping the study. Despite this, there was sufficient disquiet in the hospital that new patients in future were no longer referred to Green for their care. Unfortunately, he continued to follow his existing patients without treatment; the study was never formally stopped. As he published nothing on his study after 1974 (22), it could be argued that it was no longer research but rather aberrant clinical practice, though this would not lessen moral responsibility towards his patients.

The first accurate report on the outcome for women was in 1984, when McIndoe and colleagues independently analysed the results (23). The number of women with untreated or under-treated cervical CIS who subsequently developed invasive cancer was 29, with 8 deaths. In addition, Jones reported on 5 women with vulval CIS followed without treatment (17); all 5 developed invasive cancer and 4 died from their disease. A subsequent re-examination of all the material on cervical CIN3 showed that 43 women developed invasive cancer and 10 women died among those who were untreated or under-treated (21); among those with a diagnosis of microinvasive cancer, a further 6 women died (18). Altogether, in the order of 20 women died from their disease as a result of this study.

The Indian study was apparently monitored internally. It did have an end date, but no stopping rules were mentioned. The reason for monitoring and stopping in this case would be that, though the specified endpoint was CIS, a proportion of women might develop a more advanced lesion by the time of diagnosis. CIS is relatively easily treatable by removing or destroying the lesion; invasive cancer requires hysterectomy or more extensive treatment and there is a risk of death.

In the first report, at 84 months, 18 cases had progressed to CIS and 4 to "early invasive cancer", though there were no deaths as a consequence of the study (4). In the final publication, 75 women had a lesion that progressed to at least CIS, but no information is given about invasive cancers (5). According to the WHO case study (3), 71 women developed malignancies and in 9 the disease had already spread to other parts of the body. (In the unpublished Annual Report,

1985-86, of the Cytology Research Centre in New Delhi, 71 cases had progressed to malignancy (at least CIS) of which 7 had microinvasive disease and 9 had a diagnosis of invasive cancer (24)). In contrast to common practice, the term "malignancy" was used in all these sources to include CIS. Again, the information in the WHO case study differs from that in the published papers. It is similar to the Annual Report, but that report does not mention spread to other parts of the body.

Comparison of exploitation

Exploitation is said to occur when a person benefits by taking unfair advantage of someone else. This concept has been widely used to evaluate the ethics of intervention studies, especially in resource poor settings (25).

The women in the New Zealand study were taken unfair advantage of because they did not consent to being included in a study of the natural history of CIS that was potentially harmful to them. The benefit to the investigator, Green, was not monetary but could be counted in terms of scientific status. He travelled around the world presenting papers on his unconventional views.

For the women in the Indian study, the answer is less obvious. The setting in which they lived, in which cervical screening was not normally available to them, implies that they were vulnerable to being taken unfair advantage of. But apparently they did consent, and they did receive cytological screening and referral for treatment for CIS that would otherwise have been unavailable. Indeed they benefited from being in the study, apart from the burden of follow-up. Even the women who developed invasive cancer were likely to have been treated earlier than if they had presented with symptoms. Wertheimer (25) makes a distinction between taking advantage of an unfairness (compared to other countries or populations) and taking unfair advantage. The situation of these women in Delhi was "unfair" compared to the situation of women in, say, New Zealand, though in these terms the women were not exploited. Nevertheless it would be wrong to ignore the source of unfairness: the yawning gap between rich and poor countries (26). The history of this inequality must also be recognised: Britain treated India as an "extractive colony" from which it attained riches and India suffered (27).

The benefits for the investigators were scientific status and the advancement of knowledge. It is pertinent that the study was undertaken by the Cytology Research Centre, Indian Council of Medical Research. There is less room for exploitation in an unfair situation when a study is responsive to local needs and is conducted by members of the local population (28).

Discussion

The New Zealand study has become a paradigm for unethical research for good reason. The dangers of the study were evident from the start and it should not have been allowed to proceed unless it had been carefully and independently monitored and stopped; there was no informed consent; the concerns raised by other doctors were not properly

addressed; and many women developed invasive cancer which required aggressive treatment either with radium and radical hysterectomy or with radiotherapy, and around 20 women died. By contrast, the *end point* of the Indian study, CIS, was the *starting point* for the New Zealand study. There was informed consent, though it was not in writing. In the Indian study, the great majority of women whose disease progressed were treated at the stage of CIS, when treatment did not entail aggressive interventions. A few did progress to invasive cancer - 4 according to the first publication and 9 according to the case study. The first publication from the Indian study reported there were no deaths (4), though no similar statement is made in the later publication (5). A report in the press mentioned 2 deaths among women undergoing radiotherapy. This treatment might have been required because of delays in accessing surgery at an earlier disease stage.

Why has the Indian study come in for so much criticism? I suggest three possible reasons, though there may be others that I am not aware of. The first reason is semantic confusion. The title of the first publication from the study was: *Natural history of precancerous and early cancerous lesions of the uterine cervix* (4). This was highly misleading, as it implied that women with early invasive cancer were being followed without treatment. That was not the case: all the women were diagnosed with pre-cancerous abnormalities at the outset. Similarly, the paper described the outcome - pre-cancerous CIS - as "malignancy" and as "progression to cancer". Both "malignancy" and "cancer" are here used to describe pre-cancer. This confusion is picked up in the piece in *Nature* in 1995, which asserted that "69 women 'progressed to malignancy' and had to undergo cancer treatment or have their uterus removed" (2). Thus, a closely monitored and fairly safe follow-up study, similar to those undertaken elsewhere at a similar time, may have been mistaken for a dangerous study akin to the New Zealand one.

The second reason is a concern about the quality of informed consent in a situation where many of the subjects may be poor, illiterate, and marginalised. It is alleged that the women were not made aware that their disease could develop into cancer without treatment. Because there was no written consent, there is considerable uncertainty about what the women were actually told. As described above, women were informed that their lesion "could either regress to normality or progress to a higher grade of atypicality". Was this enough, especially for women who already had high-grade dysplasia with a possibility their disease could advance to early invasive cancer during follow-up?

Lastly, there appears to be a failure in the professional care of some women. The women subjects were recruited by gynaecologists at their local hospitals, where they had gone to seek care for another condition, and they had agreed to help the gynaecologists to research their pre-cancerous condition. Yet when their disease progressed to CIS, or to early invasive cancer, these same clinicians, it is suggested, did not take steps

to ensure they received timely care. Instead such patients were sent to the regional cancer hospital which, according to the WHO case study, had a very long waiting list, so that by the time some of these women were seen by the oncologist the lesion had progressed to a higher level (3). Other commentators on the WHO case study have already raised these concerns (29, 30). If clinicians ask their patients to take part in research, they have a professional obligation to their welfare during and even after the study.

The concerns and confusion about the Indian study of dysplasia might have been resolved if a public inquiry had been held in the 1990s. Even at this stage, releasing the records of the 1997 inquiry should resolve some of the uncertainties. Judicial inquiries held in public allow all sides to be heard and the truth to be told. The Cartwright Inquiry in New Zealand has, in the long run, had major beneficial effects on research ethics and clinical practice. It led to the establishment of a Health and Disability Commissioner's office with legal authority to investigate patients' complaints (31). Other important developments included patient advocates, new research ethics committees with half lay membership independent of the institutions conducting the research, and establishment of bioethics teaching in medical schools (32). Bioethicist Carl Elliott has singled out the Cartwright Inquiry for the magnitude of its positive influence on research ethics (33).

In India there have been more recent and persistent debates about the ethics of randomised trials of cervical screening using different modalities (34). There are important arguments on both sides of that debate. A public inquiry would allow them to be heard and weighed up.

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Manufacturing the truth: From designing clinical trials to publishing trial data

MARGARET WHITSTOCK

Abstract

This paper expands on some of the points made by Deepak Natarajan on techniques used in designing clinical trials of new drugs to ensure favourable outcomes. It also considers the nexus between the manufacturers of new drugs and the publishers of medical journals in which edited versions of these favourable outcomes are presented to the medical fraternity.

The argument will be illustrated by referring to the clinical trials of rofecoxib (Vioxx®) and etoricoxib (Arcoxia®). Both these drugs are COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) manufactured by Merck & Co. Because of the unparalleled access to Merck's internal confidential documents, due to the subpoenaing of these documents by government and private individuals in civil and criminal actions, we are still learning about the company's unconscionable acts. What we learn can inform our judgement concerning published reports of both new and old drugs.

The randomised controlled trial in the research process

Most national jurisdictions require that a new drug must demonstrate safety and efficacy via at least one randomised controlled trial (RCT), as this is deemed the most scientific method to evaluate a new drug. In the USA, for example, the only clinical trial format that is acceptable for demonstrating safety and efficacy is the RCT, and the US Food and Drug Administration (FDA) will not approve a new drug that has not been evaluated in this format.

However, in practice, this sought-after objectivity is shown to be an artifice. For a pharmaceutical manufacturer, conducting clinical trials of a new drug is a tactical exercise to support the approval to market that new drug. As an eminent

epidemiologist, Alvan Feinstein, has said: "A randomised clinical trial is designed and analysed according to strategic policies about what questions the trial is intended to ask, what answers are to be obtained, what is to be done with the data, and who is to be convinced by the results" (1). The selection and definition of the clinical problem, the variables to be evaluated, the participating subjects, the procedures and measuring techniques, the nomination of what will be considered as an outcome, the statistical analyses to be performed, and the interpretation of those analyses – all of these are made from a position of pre-specified interest (2).

This paper discusses some of the clinical trial techniques identified by Natarajan (3) in which pre-specified interests influence how an RCT is designed and reported:

1. comparison with a treatment known to be inferior;
2. non-compliance with the recommended dosages of comparator drugs to the advantage of the trialled drug;
3. choosing to submit for publication only the selected endpoints that show the trialled drug to advantage; and
4. choosing to submit for publication only favourable subgroup analyses.

The relationship between manufacturers and medical journals

During the development of a new drug, manufacturers sponsor (or act as authors of) articles on the clinical trials of the new drug, and these articles are submitted to medical journals. Publication of these articles acts as an essential tool for advertising to the medical community who will be the future prescribers of the new drug. Richard Smith, a former editor of *The BMJ*, considered that medical journals are "an extension of the marketing arm of pharmaceutical companies" (4). To illustrate, at an estimated cost of up to US\$ 836,000, Merck & Co. purchased 900,000 reprints of the VIGOR trial article from the NEJM to circulate to doctors to promote Vioxx® (5,6). Wilson (7) argues that in the public interest, the potential for capture of medical journals represented by this commercial role must be acknowledged and addressed.

Sometimes articles are not submitted for publication until after a new drug is granted regulatory approval to market (8,9), as holding over publication until post-approval reduces

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