FORSKNINGSETISKE KOMITEER

De nasjonale forskningsetiske komiteer
Prinsens gate 18
P.b. 522 Sentrum, 0105 Oslo
Tlf.: 23 31 83 00
Faks: 23 31 83 01
www.etikkom.no

Brækhus Dege Advokatfirma ANS
P.O. Box 1369 Vika
0114 Oslo

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Ethical evaluation of NorChip's project in Bukavu, Congo

The National Committee on Research Ethics in Medicine (NEM) hereby refers to the letter of 8 February 2006 from the law offices of Brækhus Dege, which are representing NorChip AS. In the light of previous statements from NEM, and NEM's then chairman Georg Høyer concluding that NorChip's project in Bukavu, Democratic Republic of Congo, ought not to have been recommended in the research ethics advance evaluation, the law firm asked the Committee that it either:
a) rescinds its previous decision on the basis of erroneous procedure, or
b) undertakes a new evaluation of the case after a sufficient illumination of all relevant circumstances and a determination of the correct facts in the case.

At its meeting in March 2006, the NEM (including new members and a new chairman from January 2006) resolved to take the matter up for renewed evaluation. The final evaluation, which follows below, was considered by the Committee in its meeting of 16 May 2006.

In what follows, the Committee restricts itself to a retrospective evaluation of the circumstances on which an advance evaluation is based. In this case, this means that we will also be commenting on the feedback that NorChip has provided regarding follow-up and implementation.
Finally, the Committee will comment on some objections regarding procedural errors.

I Factors of significance for the ethical evaluation of the project

1. The scientific objective of the study

The NEM considers that the scientific objective is unclear in the research component of the project, including the way it is presented retrospectively by NorChip AS. This means that it is also difficult to test the scientific conclusions.

In previous minutes from a meeting in the NEM (22 September 2005), it is pointed out that the purpose of the study was changed from an epidemiological study to a purely comparative methodological study. The NEM's point in this statement is not that the methodological comparison is a new objective in the study in question, but that the project was originally presented as an epidemiological study, which was abandoned by the project management after feedback from the Regional Ethics Committee (REK; confer letter to REK Vest of 29 July 2003). In consequence of this, the project also received a new title. The reason why the NEM points this out is that the Committee considers that this change of purpose is of relevance to the evaluation of the utility or the necessity of performing the study in question in Congo. A comparison of different methods does not demand the Congo as a study site. In this connection the committee would point out that, even if the project management, in the aforementioned letter to the REK, had not abandoned the idea that the project in question was an epidemiological project, there still remain statements from project management that maintain that the study also had an epidemiological aim. Among other things the final report says that an aim of the study was "to document that the incidence of cervical cancer is a major problem in Sub-Saharan Africa". This point is repeated in various ways in the extract from TV2's interview with NorChip that was forwarded to REK Vest by the project management (there it is said that the study is being undertaken among other things to document that "this is actually a major problem in the area"/"how serious cervical cancer is in this area"), and the same formulae also recur in a description of the project from project coordinator NN of the Norwegian Association for Gynaecological Cancer Patients) on 17 March 2006. The committee does not doubt that cervical cancer is a serious problem in Sub-Saharan Africa, but given the way the study in question is designed, and the way in which the women in the project have been selected, it is misleading to say that this study can document the incidence and gravity of the condition in question, whether in Congo or in Sub-Saharan Africa generally.

In the final report (page 2) the purpose of the study is stated as being threefold:

1) To document that the incidence of cervical cancer is a major problem in Sub-Saharan Africa.
Commentary:
As mentioned above, this is not demonstrated by the study, because only preinvasive stages (cervical dysplasia, not cervical cancer) have been diagnosed and treated in a not clearly defined group of women in an area of the Congo (inclusion criteria and exclusion criteria are not clearly defined; what was the incidence of dysplasia and cervical cancer in group of women who were not offered participation in the study?).

2) To document what technology is most favourable for preventing cervical cancer in a low-resource setting such as the Congo.
Commentary:
The study was unable to answer this too. It is only cervical dysplasia stages that are treated, and it would be unethical to follow the women without the excision of cervical dysplasia in order to see which women would have developed cervical cancer (not everyone with CIN 2+ or the types of HPVmRNA that PreTect HPV-Proofer can detect, would with certainity have developed cervical cancer). What the study *has* been able to answer, on the other hand, but which was not stated as an objective of the study in this report, is what the HPV incidence (DNA and mRNA documentation) was in the group of women who participated in the study, and how many with positive histology (though with sources of error due to insufficent biopsies in certain individuals, without the transformation zone being included) or cytology, who had active gene transcription (mRNA expression) of which HPV types in the cervical test.

3) To give the participating women a thorough gynaecological examination and the best possible treatment to prevent cervical cancer**.**
Commentary:
This is not a testable scientific question and is therefore not part of the scientific purpose of the study.

A lecture by NN appended to the final report to REK Vest cites three objectives for the study:

1) To compare colposcopy, cytology from the cervix with HPVmRNA E6/7mRNA with histology as the gold standard.
Commentary:
This is done in the study.

2) To chart the current situation with regard to cervical cancer in Congo**.**
Commentary:
This is not documented in the Congo study by means of a scientifically testable or acceptable epidemiological method, see above.

3) To train local medical personnel in clinical gynaecology**.**
Commentary:
The NEM has not found documentation of the training effect of the two weeks with nine days training by Dr. Berle that were divided between three hospitals (confer final report and annex 5 to this). If this was supposed to be a part of the scientific aim, we would expect the documentation of clearly defined outcome variables. Is, for example, colposcopy currently being used by the local doctors in the centres that participated in the study, in the screening for preinvasive lesions in the cervix? NorChip's study showed a high proportion of "false positive" colposcopy results in relation to CIN2+. This does not necessarily mean that local

doctors have not received good enough training to interpret colposcopy findings (which are unspecific), but it can also be connected with for example frequent inflammation or infection of the cervix in the population being examined. What diagnostic tools do the doctors have in future on which to rely if preinvasive lesions are to be diagnosed? Where are the women offered minimally invasive surgery for preinvasive lesions in the future? The NEM cannot see that it has been documented that the local doctors have been trained in this, nor that there is equipment available with which to treat the preinvasive lesions. In the information that NEM has available, the Committee has not found any documentation that the brief training of health personnel has had any effect on the further examination and follow-up with regard to preinvasive cervical lesions in women who did not participate in the study.

The letter from Brækhus Dege (page 5) says that the point of the project was "to demonstrate the utility of molecular pathology and/or the PreTect HPV-Proofer in a high-risk population in Africa".
Commentary:
The NEM cannot see that any cost-benefit analysis has been undertaken in a scientifically testable manner in the study. The study shows, however, associations between HPV types (mRNA expression as a sign of active gene transcription) and histologically demonstrable serious dysplasia. This latter is in conformity with the feedback to REK Vest on 29 July 2003: "the project wishes to compare a molecular-biology method with more traditional methods such as cytology and histology to demonstrate various stages of cellular changes" (page 1). The NEM's evaluation is that this methodology component ought to have been performed in a country other than Congo, for reasons to be explained below.

2. The value of the research project for the population being researched

The Helsinki Declaration requires that all research projects must justify themselves by demonstrating that "the populations amongst which it is carried out have real chances of benefiting from the results obtained" (Paragraph 19). It is important to note that what the Helsinki Declaration is here talking about is the benefits from *the results of the research*. That the people included may derive benefits from health services offered *in combination with* the research, is not regarded as a sufficient justification for undertaking a research study on the population group in question. It is of extra importance if the participants in the study are regarded as belonging to a particularly vulnerable population group; that is, that they are less able than others to safeguard their own interests. There are several factors that suggest that the women to be included in the study in question in Congo must be classified as belonging to a vulnerable group, for example a high degree of illiteracy, poverty and the fact that the community of which they are a part is not conversant with modern medical concepts. It is an internationally accepted research standard that research should not be performed in particularly vulnerable groups if the research in question can just as well be performed on less vulnerable groups (confer for example the research ethics guidelines of

CIOMS – Council for International Organizations of Medical Sciences, Guideline 13). The justification for this is not only preventing the welfare of extra exposed groups becoming subordinated (consciously of unconsciously) to other considerations (such as the interests of the researchers themselves), but also the avoidance of all *suspicion* that this might be the case, since that would weaken public trust in research generally and thereby also people's willingness to participate in research.

- *no present-time health benefit of the methodological evaluation for Congo's population*

As regards NorChip's project in Bukavu, the NEM cannot see that there is sufficient justification for performing what is the specific *research* component of this project (the comparative methodological study) in Congo. One of NorChip's arguments for performing the study in a developing country (confer letter from NorChip to REK Vest of 29 July 2003, section 2, plus the commentary to Paragraph 19 of The Helsinki Declaration in the letter from Brækhus Dege), is that if the molecular-biology method detects almost 100% of the cellular changes that are diagnosed by histology in Congo, this is "good evidence that the method can substitute for cytology and histology, both of which require considerable pathology expertise", which is obviously in short supply in Congo.

The committee sees that this could be an argument for adopting the test in Congo when its evaluation is complete, provided that this was otherwise desirable and possible in the Congolese situation. The NEM cannot, however, see that this is an argument for the actual *evaluation* of the test being done in Congo. The committee also notes that, in its interview with TV2, NorChip says that their test has been documented as being the optimal test for reducing cervical cancer "together with cytology", and that "it remains to be seen" whether we "in the future can obtain documentation showing that the traditional cytology can be replaced" by their or other tests. Therefore, it is only in a hypothetical future that countries with no expertise in performing cytology/histology might be able to benefit from the results of the research in question.

It is the same situation that underlies the previous statement from the NEM's chairman that the project is in breach of the Helsinki Declaration, because it concerns "trials of a diagnostic test that is not really being used for screening purposes, but for testing with a view to marketing in the industrialised countries" (confer minutes of Working Committee meeting on 1 June 2005), a statement contested by Brækhus Dege. The committee cannot see that this statement can be interpreted as claiming that the test "cannot be used for screening purposes" (see section 2.4 of the letter from Brækhus Dege). The point is that the test, *in the project in question*, is not a part of a screening study, but is being used in a study for further testing and evaluation of a diagnostic method that the project management states is "part of the technical documentation required for CE marking" (confer minutes). As regards the statement that this testing is done "with a view to marketing in the industrialised countries", the point is to show that it is – at any rate for the present – only the industrialised countries that have the ability to make use of the type of test in question here, and to conduct

the kind of screening programmes of which the tests are to be a part. This is confirmed by the project management which, in a letter to REK Vest (29 July 2003) says that in principle NorChip intends to earn money in Europe and only expects minor revenues from Africa in the initial years (section 3). In its letter to REK Vest dated 17 November 2004, the project management admits that the preconditions for screening are not present in Congo today, but claims that a molecular-biology method can be used to identify women whom doctors can learn to treat, something that NorChip has a training plan for. They also say that they think it is important to undertake pilot studies so that they will be "ready to consider the introduction of a screening programme when the country is ready for it." Regarding its own test, NorChip says that they have a technology under development that we hope will reduce the production costs and thereby the price to a wholly different level." These statements show that it is uncertain whether the Congolese health service will be able to benefit from molecular-biology tests, and that in the best case this is something that lies in the future. This is of relevance for whether the project satisfies the criteria of the Helsinki Declaration Paragraph 19 (see above) and Paragraph 30 (see below).

- *is knowledge of the risk a health benefit?*

In the study protocol it is said that the women included will have the opportunity to be evaluated for the risk of developing cervical cancer. This is also stated in the letter from Brækhus Dege (in their comments to Paragraph 8 of the Helsinki Declaration) as proof that the included women have derived benefit from the research. In an amplifying commentary that NN sent to REK Vest on 12 June 2003, she writes that NorChip hopes that the examination can help to disseminate information about cervical cancer and how the risk can be reduced, and thereby induce more women to present themselves for a gynaecological examination. It is also explicitly stated, however, that this will be a financial burden on the women, and that some will not be able to afford it.

Even in prosperous countries, there is a discussion of the value of screening for risk factors and the gain contra damage of telling people that they have an elevated risk of contracting a particular disease. There must be all the more reason to ask how useful and desirable it is to screen for preinvasive conditions and give women information that they have an elevated risk of developing cervical cancer, in a country with Congo's material situation. As described also by the project management, the Congolese health service is facing major challenges in meeting the very fundamental and neglected health-service needs of the population. As regards the individual woman, there is reason to ask how she is supposed to make use of the information about risk and how better to prevent cervical cancer, if she is even less able than Western women to understand what an elevated risk actually means and if she cannot afford to go for an examination, or if both she and the health service have more urgent things to do. When research is done in countries and population groups with limited resources of their own, it is decisive that this research be directed at the relevant country's or population's group's own health needs and priorities.

- *can the diagnostic test be made available to and usable by the population?*

Standards of international research ethics maintain that a precondition for saying that research is oriented towards the health needs of the country in which the research is being conducted, is that population group or community involved in the study is able to derive benefit from whatever might emerge from it, inter alia that any intervention or product developed through the study in question, or knowledge generated, is made available to the population group or community in question by the sponsor or researchers (confer CIOMS Guideline 10). It is of especial importance where the authorities in the country concerned lack the resources themselves to ensure this availability. This is related to Paragraph 30 of the Helsinki Declaration, which has a similar scenario, but with a restricted focus on the individuals who have participated in the study. It may appear as if the project management has misunderstood the content of Paragraph 30 when, in their commentary on this paragraph, they maintain that they have complied with it, on the grounds that "the same two tests and the same analyses have been done for all patients". The relevant paragraph discusses what is to happen *after* the study has been concluded; namely that all patients who have participated in a study in which research is combined with health services must be "assured that, once the study is completed, they will benefit from the diagnostic, therapeutic and preventive means whose superiority will have been shown in the study". This means, therefore, that if NorChip considers that the study documents that it is their test that has the highest prognostic or diagnostic value, then it is this that shall be made available to and applicable for the women included in the study, and the community from which they have been recruited. The NEM cannot see how it has been at all possible for NorChip to have met this criterion in relation to the study in question, inasmuch as the prevailing situation in Congo means that general availability and applicability of molecular-biology test can only be realised, if at all, in an uncertain future. The committee therefore considers that this is an argument for the view that the comparative methodological study ought to have been conducted in a country in which thus type of molecular-biology test is already part of the established health service. The current recommendation in Norway regarding the use of HPV-tests (DNA or RNA-based) is that primary screening with HPV is discouraged, other than under scientific supervision and together with cytological sampling (confer the guidelines of the Norwegian Gynaecological Association and the Cancer Registry of Norway).

Given the material produced by the project management, the NEM cannot see that there exist sufficiently good grounds for performing the study in question on a vulnerable group in Congo.

It can be argued that studies should be performed in a low-resource country despite the fact that they could also be performed elsewhere, provided that the included persons have given informed and voluntary consent, the study does not involve any costs or negative consequences for the included persons or their community, and the project also has an aid aspect or some multiplier effects that bring positive consequences to the country. As regards

the project in question, however, the NEM considers that the informed, voluntary consent can also be questioned, and that there are several potential harmful effects both for the included women and for the reputation of the research and the health workers involved in it.

3. Was the consent sufficiently informed?

Paragraph 22 of the Helsinki Declaration specifies what kind of information is to be given to those whose inclusion in a research project is being considered (confer CIOMS Guideline 5). The information that the project management themselves have provided shows that the information given to the women in connection with the Bukavu project does not satisfy the requirements of this paragraph. In the first place, the available material provokes the question whether the women were given "comprehensive information" about the *purpose* of the study. The information leaflet says merely that the purpose of the study is to "examine women for serious diseases by means of old and new methods of analysis". The letter from NorChip to REK Vest of 29 July 2003 comments that doctors do not see the actual leaflet as of great importance, but that they will provide thorough information about "the consequences that sampling may have". The main points of the information stated in the letter from NorChip of 17 November 2004 also discuss solely the consequences for the women of the examination in question. The NEM finds no documentation that participants in the study have received information that they have lent themselves to a study designed to evaluate different methods of screening for cervical dysplasia. In its reply to Onsrud's letter (17 November 2004), NorChip takes his statement that the women did not understand that they were part of a methodological evaluation study, but merely thought that they were to get a gynaecological examination of best European standard and thereafter treatment, as evidence that their information got through. This, too, indicates that NorChip did not give, nor did it think it important to give, information that the purpose of the *research component* of the project in question was evaluation of diagnostic methods, and not treatment. The available material contains some statements that may be seen as justification for not providing this information. In the annex to the application (12 June 2003) to REK Vest, NN says that there is widespread illiteracy in the general population and that it is difficult to convey an understanding of the analysis samples to be taken. The letter to REK Vest of 17 November 2004 also states that it was "difficult in the given situation to give them a better introduction to the background to the examination". The NEM is inclined to think that these statements demonstrate some of the problems in performing this kind of high-tech study in countries with high illiteracy rates and lack of familiarity with modern medicine. The Committee considers that the problems encountered in making the purpose of the study comprehensible to its participants is an argument *against* conducting it in the Congo, so long as there are no other weighty reasons for conducting the research project in this particular area.

Nor does the NEM find it to be documented that the women were informed (prior to being invited to lend themselves to the study) that cervical conisation (also done in the modern

manner with minimally invasive surgery), which is the recommended treatment for serious and persistent cervical dysplasia, is associated with increased incidence of miscarriage and premature birth in women who become pregnant after the surgery. The NEM does not know how many women in the study were still fertile, but since their average age was 37, the Committee assumes that this applies to a high proportion of women. The NEM is aware that the consequences of any cervical conisation may be a complex matter to include in an invitation to participate in the research study, also because it is not known how many women have pre-invasive cervical lesions and thereby in need of treatment. The Committee considers, however, that this aspect also illustrates the problems with conducting the study in Congo with its generally low educational level, and probably no opportunity to follow up the women with regard to cervix length in the course of any future pregnancy (with inter alia ultrasound screening and perhaps an offer of cervical cerclage to prevent late miscarriage if the women demonstrate pathological shortening of the cervix).

Paragraph 22 of the Helsinki Declaration also states that participants must be informed about "financing, possible conflicts of interest, membership of the investigator to one or several institutions", which was not done either in the project in question in Bukavu. In the annex to the application of 12 June 2003, NN justifies this deliberate omission on the grounds that the information that a foreign firm is involved in the study will in all probability induce the women to consent, "because they will see this as salvation from the difficult situation in which they are living". In his letter of 17 November 2004, NN says that the women in Congo, who are "by nature highly emotional and creative", "will rapidly let their imaginations run riot in relation to the fact that a European company was participating in the project". Among other things they would "persuade themselves and others that they both have undergone great suffering and also need unrealistic financial support, food and treatment from NorChip." In addition to the fact that these statements contain a generalisation about and stigmatisation of human beings that is hard to defend, the NEM would maintain that, to the extent what is said here is correct, this would be yet another argument for *not* conducting this kind of European industrially financed research in the Congo. Even if the women who are invited to participate in the study in Congo might see a personal advantage in lending themselves to the gynaecological examination of which the methodological trial was a part, it can equally well be envisaged that there exist Congolese women who for various reasons do not want to make themselves available to a European firm that wants to evaluate a diagnostic test that neither they themselves nor their country can benefit from in the near future. The fact that, according to the project management, local health workers and leaders in Congo consider that the women, if they are not so already, "ought to be grateful for being allowed to participate in such a thorough examination" (confer the letter from NorChip of 17 November 2004), is not an argument for omitting to give the Congolese women "comprehensive information" so that they can make an independent, informed choice whether to participate or not when they are invited to lend themselves to a research project.

In addition to the requirement to convey comprehensive information to research participants for the sake of the individual's self-determination, it is also important to preserve public trust in medical research in general. Revelations at a later date, for example that a foreign company with its own commercial agenda took the initiative for and/or sponsored a research project without the participants being informed of this, are liable to evoke suspicion and distrust, however good the intentions of the project in question may have been. If it is true, as the project management say in their interview on TV2, that "there is hardly any population group in the world that is more suspicious and sceptical of foreigners than the population in this part of Congo", this should be all the more reason to pay attention to this point in relation to the project in question in Bukavu.

4. Degrees of voluntary consent

It is a recognised issue in research ethics that the degree of voluntary consent in relation to participation in a research project is reduced when the research is combined with an offer of medical assistance to which the participants would not otherwise have enjoyed access. The information leaflet for the study in Bukavu tells the women that "they will have the opportunity to be more thoroughly tested for a serious disease than the individual out-patient clinic is in a position to offer its patients today", and also "have a greater chance of being treated for a serious disease" than the Bukavu hospitals are currently able to offer. Also in its letter of 17 November 2004, NorChip maintains that many of the women cannot normally afford to report for examination, and will now make use of the chance of a free examination that the "bush telegraph" will have told them about. That combining research with health services in low-resource countries creates an extra challenge in relation to preserving the volunteer aspect of participation in this research, does not mean that this kind of research cannot be accepted at all. There is, however, reason to insist even more strongly on the need to provide comprehensive information, a realistic opportunity to decline and to withdraw from the study, and reassurance that doing so will not prejudice any necessary medical treatment and follow-up. In addition, it is a recognised principle that this type of research be subjected to extra stringent requirements as regards both demonstration of the probability of health benefits accruing from the research for the population group that lends itself to the research, and minimisation of the risk. As described above, the Committee cannot see that the project in question has a sufficient utility for the population group from which the participants were recruited. The NEM also questions whether the risk in the project in question was sufficiently low, see the following section.

5. Were the women exposed to unnecessary risk in that biopsies were taken from everybody?

NorChip's letter of 17 November 2004 argues that taking a portio biopsy of all the participating women was in part methodologically necessary, in part that it would accelerate

any necessary treatment, since it would be easier to get the women in one more time if there was a clear need of treatment. Many of the biopsies would, therefore, have a positive significance only for the project and not for the individual women. That having a biopsy performed can be painful for some women may in itself be a reason not to expose women to it, unless it is important in the interests of the women themselves, or else serves a research purpose about which the women have been comprehensively informed and consented to. The most important objection to performing biopsies on all the women in the project in question, as long as this is not necessary for reasons of the individual woman's health, however, is what the project management also says they have borne in mind throughout: the high incidence of HIV and hepatitis in the area. In the letter from NorChip of 17 November 2004, NN says that on the basis of her knowledge of the dangers of infection, she imprinted on the doctors how essential it was to inform the women of the importance of sexual abstinence for at least a week after the biopsy, due to the increased risk of infection caused by an open wound on the cervix. The Committee doubts, however, that this is adequate protection for the individual woman in a part of the world where sexual abuse is widespread and fear of rape is justified. That performing biopsies on participating women can lead to (and has led to) some women in need of treatment being discovered who would not have been detected by other methods is naturally a gain, but in a research-ethics evaluation it is nevertheless far from obvious that this outweighs the risk that some of the women who did not need treatment become infected and fall sick because participation in the study in question led to their having an unnecessary lesion on their cervixes. If the performing of biopsies on everyone was required for methodological reasons, the Committee would argue that this is a reason for conducting the study somewhere with a lower incidence of HIV and hepatitis.

6. Follow-up of the women who were included in the project

One of the NEM's previous objections to NorChip's project in Congo was that the opportunities for follow-up of the included women were unsatisfactory, due to the political and material situation in Congo, and that the project should therefore have been conducted in a country where conditions were more favourable to the follow-up of participants (confer minutes from the NEM meeting of 22 September 2005, plus the statement from the NEM chair to TV2).

As far as the NEM can understand, the project management confirms in its own material that the follow-up of the participating women was problematic in the conditions prevailing in Congo. For example, the project management admits in its letter of 17 November 2004 that it took a long time before the test results were available and treatment offers made. The reason for this was cited as pressure of work for the external project staff involved, plus military attacks and instability in the area, leading to foreigners having to be evacuated and the training of doctors and the treatment of women having to be postponed. It is also stated in connection with the fact that one woman was already dead and many not traced when Dr.

Onsrud came and was to begin the treatment, that NN could only note that "the doctors present did not take the initiative for any direct treatment of the woman who was aged 60", and that the local gynaecologist who had been told about women needing treatment, had clearly "not gotten around to doing anything about the tracing of these women". It is also said that NorChip itself lacked sufficient medical expertise to be able to evaluate what was needed to perform acceptable surgical treatment in Congo, and they were therefore depending on the parties undertaking the treatment being able to assess what would probably be impossible to get hold of in a war-ravaged country. As the NEM sees it, this illustrates some of the problems with being responsible for research in a context quite different from one's own. The project management's defective control of follow-up is understandable, but strengthens the argument that the study ought to have been conducted in a country with better conditions for follow-up on the part of project management. Also in the final report, it is stated that the implementation and follow-up in the study was time-consuming and unstable because of poor infrastructure, war and looting.

That all the identified women in need of treatment, except for the one who died, have now received treatment, is very gratifying. The NEM has been informed that the 16 women with histologically detected CIN2-3 lesions in the cervical biopsies have been treated with conisation of the cervix (three or four were treated despite negative biopsy, and were subjected to conisation because of positive cytology/HPVmRNA and probably badly-performed biopsy; the cone material subsequently confirmed a serious dysplasia diagnosis. One cone result is missing, confer final report page 7). On the basis of the available material, the NEM cannot see that there exists any plan for further follow-up of these women, for example offers of re-cone biopsy of women without "free rim" on the cone material etc.

An obligation to follow-up will also cover those who have an elevated risk demonstrated. This applies firstly to the women who were satisfactorily treated ("free rim" on the cone material) and who have an elevated risk for new preinvasive or invasive cervical pathology. In Norway and other countries with available screening systems, women in this category are offered follow-up in the form of cytology screening. The NEM questions how NorChip is going to follow these women up in Congo, where cytology is said not to be available. The follow-up problems are not less in relation to the other group of women with elevated risk of developing cervical cancer, and who, according to the final report should therefore be followed up "with the same intensity as CIN 2 + histological": women with positive HPVmRNA E6/7 without histologically demonstrated CIN2-3 (n=11, confer page 7). If there does not exist a concrete plan with a realistic possibility to follow up these women from the study, the NEM considers that this is another argument that the study ought not to have been conducted in Congo. As previously commented, there is reason to ask whether it is possible and/or desirable for the Congolese health service to use its scarce resources to monitor risk conditions.

In an ethical evaluation of a research project prior to study start, it is important to consider not only whether it is *possible* to implement subsequent treatment and follow-up or not, but

also *how difficult* this may be. The harder it is, and the longer it takes the researcher to discharge his moral responsibility to follow up the medical problems uncovered by a research project, the greater chance there is of public confidence in the researcher, research in general and the health workers participating in the research being weakened.

Another aspect of the follow-up requirement for research projects is that, as previously mentioned, after the end of the study the participants must be assured of access to the method or methods that the study as documented as being the best. The difficulties for the project in question in meeting this requirement are discussed above.

II Procedure of the NEM

Brækhus Dege argues erroneous procedure on several points.

The NEM both can and ought to comment on individual projects, whether on enquiry or on its own initiative, when individual projects raise questions of principle, or for other reasons that are considered to be relevant to further reflection and discussion of research ethics. In the case in question, the NEM has commented on a project at which the Committee thinks there is reason to direct critical questions, and from which there may be something to learn for the future.

The project management obtained their recommendation from REK Vest and were to have implemented the project in conformity therewith. The NEM has not undertaken "a concluding evaluation of the project", as claimed by Brækhus Dege, but has supported a statement that the project "ought not to have been recommended" (confer Høyer on TV2). The final report from the project therefore had no significance for this statement and evaluation.

The NEM does not make individual decisions within the meaning of the Public Administration Act, and is therefore not subjected to the strictest rules for procedure consequent on that Act. The Committee nevertheless wishes to follow these rules as far as possible, and admits that it certainly has room for improvement in relation to a documentary basis for the Committee's evaluation. As regards the Committee's evaluation in the case in question, however, it is incorrect that this is primarily based on the controversial letter from Mathias Onsrud that NorChip considers contains erroneous information, and that NorChip's reply is not taken into account. It is first and foremost material from the project management itself that constituted the basis for the NEM's earlier statement that, in retrospect, it appears that the project ought not to have been recommended. The controversial letter from Mathias Onsrud was the reason why the NEM (via its chair, to begin with) wanted to take a fresh look at the project, but the letter was not decisive for the conclusion that the project ought not to have been recommended.

Brækhus Dege also comments on the statement that the lack of a research ethics committee in Congo "should have occasioned further caution in recommending the project (confer minutes of the meeting in the NEM 22 September 2005). The NEM agrees with NorChip and the law firm that a country's not having an ethics committee is not in itself an argument for non-recommendation of a project contemplated in that country. It was not, therefore, this that the Committee wished to communicate with the statement in question. An important reason why a research project should be given an advance evaluation by an independent, broadly-composed research ethics committee in the country where the study in question is to be carried out is that the evaluation of and balancing between the potential benefits and the possible risks or damage that a project may bring about should be undertaken by a body that both knows the context in question well and does not itself have interests in the project in question. That health authorities and collaborating doctors in a developing country approve a project, as was the case with the Congolese project, cannot be regarded as a guarantee that the interests and welfare of those included in the study will be adequately safeguarded – as these bodies may have their own interests in the implementation of a project (not least if the project involves important training, supply of equipment, co-authorship etc. as was also the case in the research project in Congo). A research-ethics evaluation by a committee in Norway can provide an independent perspective. On the other hand, the sensitivity to context, which is often a precondition for being able to evaluate benefit and risk in a different geographical, political and cultural situation, will often be unavailable when the evaluation is done by another country's ethics committee. When the NEM takes the view that the REK ought to have displayed "extra caution" in the recommendation project, since the project in question was to be conducted in a country without an independent research ethics committee, this was first and foremost an expression of the fact that this kind of situation demands an extra careful evaluation of the value and possible harmful effects of the project for the population in question. One possibility is the use of consultancy assistance if the committee does not itself have members with experience from similar projects and contexts. This possibility, moreover, applies to all kinds of research projects that are considered by the REK system, not just projects in developing countries.

Conclusion

In a research-ethics evaluation it is important to point out all factors that may cause reduced protection of the participants' interests, and factors that may contribute to create public distrust of research, whether justified or not. The trust factor is particularly important when a research project involves the health workers on whom the participants will continue to depend for necessary medical assistance in the future. Much medical research has a great potential for improving the quality of life for people who need it. The NEM therefore sees it as an important task to direct attention to factors that can weaken public trust in medical research and thereby also their willingness to lend themselves to this type of research.

To sum up, the NEM would maintain that NorChip's project in Bukavu ought not to have been conducted in Congo because:

- The study has an unclear scientific purpose.

- The medical benefit of the study is extremely uncertain, both for the women who participated in the study, and in Congo generally.

- Even if a subsequent study in a suitable country that has methods for following up both cytological tests and HPV tests, such as for example Norway, would show the benefit of a HPV test (that NorChip or other manufacturers have developed), it is doubtful whether Congo would benefit from the test in the near future.

- Due to a general low level of education and widespread illiteracy, the women recruited to the study probably did not understand that they were participating in a research project and/or what the purpose of the study was. Nor did the information leaflet given to those who could read make this clear.

- Women in the study were not informed that the study was backed by the company NorChip.

- Women in the study risked being infected by HIV and hepatitis B (and other venereal diseases that are common in Congo) if they had intercourse after the creation of the open lesion on the cervix.

- The methodological comparison of NorChip's HPV test, tissue samples and cell samples was not suitable for performance in Congo, because conditions were unfavourable for follow-up and treatment of women after the samples had been taken.

- Such a methodological study for evaluating the utility of a molecular biology test should be conducted in a country in which women have a sufficient comprehension of health and disease to understand what they are letting themselves in for, and in which the country has a sufficiently developed screening system to diagnose, treat and follow up cervical dysplasia. This is not the case in Congo.

- The desire to do something positive for women's health in Congo must not be mixed up with carrying out a research project with a very uncertain objective and utility, and with potential harm to participating women.

The NEM considers that the evaluation in this letter concludes its involvement in this case.

Yours sincerely,

Beate I. Hovland
Chairperson of NEM

Knut W. Ruyter
Chairperson of Secretariat