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ETHICAL ASPECTS OF HUMAN NUTRITIONAL INTERVENTION STUDIES

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Only by undertaking studies on whole organisms, particularly humans, can we really assess the importance of foods in relation to health benefits. But, undertaking human intervention studies presents the scientist with a number of scientific and ethical dilemmas which are often in conflict. It is not ethically acceptable to undertake a human study which is not scientifically valid, so before designing an intervention study the aim of that study must be clearly defined and then the limitations of any markers of effect or practicality of execution, evaluated in the light of the original aim. Once the science of a study has been determined then the degree of benefit to both the individual and society must be weighed up against the inconvenience or risk for the participant. Nutritional intervention studies should be considered with the same degree of care as pharmaceutical trials, particularly as healthy volunteers are frequently involved who are unlikely to gain any personal benefit from the study. Additionally, when considering the biological activity of phytochemicals, especially those associated with herbal medicines, and with the development of nutraceuticals the line between nutrition and pharmacy is blurred. In Britain, human intervention studies involving healthy volunteers, not conducted within The National Health Service, must still be subject to ethical review and increasingly the use of Hospital Local Research Ethics Committees representing a wide range of professionals is being encouraged by The Department of Health in their guidelines for research governance. The ethical aspects of these guidelines are ultimately based on the Helsinki Declaration. Volunteers who take part in a study must understand the purpose of that study; to this end a full written information sheet must be provided and a verbal explanation given well in advance of the start of the intervention. Only once a volunteer understands the study can his or her consent be considered fully informed and thus have legal status.

INTRODUCTION

Much of the evidence of biological activity associated with phytochemicals has been based on cell culture studies, usually using cancer cell lines and often taking little heed of the amount or biological form presented to a particular cell type. Only by undertaking intervention studies on whole organisms, including humans, can we really assess the importance of foods in relation to health benefits. In general intervention studies on people span a wide range of interests from those assessing the benefits of novel psychological interventions, through the more pharmaceutical studies to the evaluation of what might be considered highly physically--invasive new surgical techniques. Nutritional intervention studies align most closely with pharmaceutical trials in terms of level and type of intervention.

The rules of behaviour considered acceptable or morally correct are the basis of ethics as we know it today. These moral rules make up the ethical framework under which we all should act and these are generally internationally agreed. The exact interpretation of the rules may depend on cultural and religious influences as well as national and international laws and in certain situations ones personal ethical view may be in direct conflict with those of a particular society. In considering research ethics, and more specifically the ethical aspects of intervention studies, the ethical issues become more straightforward than in the context of the wider meaning of the term. The issues associated with nutritional intervention studies may seem trivial to some people when comparing giving participants a particular food to giving a new drug as part of a pharmaceutical trials, food being assumed to be less risky. But, in making this assumption, the critic fails to see that there is no clear cut boundary between nutritional and pharmaceutical interventions and often drugs have had more exhaustive safety testing than would be applied to a novel food. Again, the physician who treats malnutrition in the elderly is making a clinical judgement based on the results of nutritional intervention studies. The earliest and most famous probably being the study by Dr James Lind started in 1747 in which he showed that scurvy could be prevented in British sailors by enforcing the consumption of lime juice. Therefore the ethical conduct of human nutrition intervention studies must be informed by the same considerations that apply to any intervention study. In this context it is useful to compare nutrition studies with the different phases of pharmaceutical trials (Table 1). All centres running clinical trials in Europe are now expected to follow Good Clinical Practice Guidelines [Directive 2001/20/EC] and so by the above argument effort should be made to implement the same recommended practices in relation to nutritional studies, particularly those involving novel ingredients, isolated food components or higher risk methods of measuring end points. It is now considered essential that all such studies should be reviewed by an independent ethical review committee made up of

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TABLE 1. A comparison between pharmaceutical trials and nutritional intervention trials. Generally the former is looking to cure illness whilst the latter is often aimed at preventing illness or maintenance of health but there is no clear cut boundary particularly in respect to nutraceuticals and functional foods.

	Pharmaceutical agent	Nutritional Equivalent?
Phase I	• compound never been given to people before	• an isolated food component may not have been given before but probably not equivalent unless given at supra physiological levels, *e.g.* nutraceuticals
	• Use a few healthy volunteers	• YES may use small numbers for pilot studies or bioavailability studies bioavailability studies
	• Safety testing - dose response	• dose response may be undertaken but not normally for safety reasons
Phase II	• Use a few patients	• ·could arise in clinical nutrition or when patient is a sources of biopsy tissue
	• Testing efficacy	• YES certainly looking for an effect
Phase III	• 100s -1000s patients	• nutrition studies may use large numbers of people but not normally patients - only potential patients as considering disease prevention
	• efficacy	• YES
	• side effects	• probably NO for whole foods but YES if studying supplements or nutraceuticals
Phase IV	• licensed drug for wider purpose	• might arise with functional foods and nutraceuticals as legislative procedures are developed

members with a range of expertise including for example legal, medical, ethical, psychological and scientific knowledge as well as people who can represent the general population who may be recruited into such studies. In the UK, committees set up for assessing work from within the National Health Service may also be accessible to other research organizations with prior agreement. Alternatively large research organizations and universities may have their own ethical review process. Guidelines on the operation of Research Governance and Ethical Review in the UK were most recently updated in 2001 [Dept. of Health for England and Wales].

APPROACHES TO ETHICAL ASSESSMENT

There are three basic approaches to ethical assessment: goal based, duty based & rights based. The goal based approach will ask whether the research is valid and the question being asked is important and novel. Integrated in to this assessment is the implicit need to judge whether the scientific approach can answer the question asked, otherwise the study cannot be considered ethical. Therefore the study must be predicated on a clearly defined hypothesis or expected outcome. When the duty based view is considered it is necessary to judge whether the researcher has considered how their work might impact on the participant in terms of any safety issues, pain and discomfort, psychological disturbance or inconvenience, and whether the value of the research is sufficient to make these impositions acceptable. Finally a rights based approach considers the rights of the individual to be fully informed about the study and for all data concerning them to be kept entirely confidential. International guidelines for the conduct of human studies were first set out in the Helsinki Agreement 1964 [Helsinki Declaration, 1964], which have been modified in subsequent years with the most recent being produced in 2000 [Helsinki Declaration, 2000]. These guidelines emphasise the importance of studies being scientifically valid if they are to be considered ethically acceptable as well as judgement being required in considering the benefit of the study compared to any risk that might be associated with the study. The emphasis on the rights of the individual has increased significantly since the first version of the Helsinki agreement. In many studies there is little benefit to the individual and much of the benefit is to society. Where the risk to the individual is low, as is the case in many nutrition studies, this poses little problem and often it is a matter of the extent to which an individual should be inconvenienced in the name of scientific progress. However, there are nutritional studies which could entail quite considerable inconvenience or discomfort to those who volunteer, such as detailed filling out of food diaries or taking of biopsy samples, and judgement as to the value of the science compared to the level of discomfort should be made. Only the individual can really assess whether they are prepared to undergo any discomfort or inconvenience and to make this judgement they need to be fully informed in advance about all aspects of the study in a manner they can fully understand. To be able to do this the study must be well planned in advance.

PLANNING A STUDY

In planning a new study the three approaches to ethical review need to be covered and to achieve this it is recommended that these steps be followed:

1. Goal Based: (i) a thorough review of previous literature; (ii) production of a detailed protocol which considers: importance of the research; study design; inclusion and exclusion criteria; validity of questionnaires; scientific validity of biomarkers; technical resources; statistical power; analytical approaches.

2. Duty Based - review of; (i) skills and training of staff undertaking the intervention; (ii) risks to individuals and time commitment involved; (iii) appropriate medical cover in case of emergency; (iv) appropriate method of recruitment; (v) necessity to use results as planned; proper storage & disposal of samples.

3. Rights Based: (i) information sheet; (ii) consent form.

Within the UK the more scientific aspects of the review process are considered to be outside the remit of the ethics committee and so need to be reviewed by a separate Research Governance committee prior to submission for ethical review. This committee will be constituted to be better

able to review the science and to have insight into the availability of resources required for the study within the institution(s) involved in terms of skills, physical and financial resources, but not to consider the more subtle ethical aspects. However, the ethics committee does require evidence that such a review has taken place to be satisfied that the scientific validity of the study has been properly assessed.

An ethical committee is most likely to focus on the following aspects of a study: (i) recruitment of participants; (ii) the consent process and information sheet; (iii) inconvenience to and safety of participants; (iv) genetic screening; (v) data protection in relation to an individuals results; (vi) storage and disposal of samples; (vii) dissemination of results.

RECRUITMENT OF PARTICIPANTS

It is generally not acceptable to recruit volunteers into studies who are in a 'dependent' position to the investigators [Convention for the protection of...]. The definition of 'dependent' in this context has to be considered with some care, balancing the feasibility of recruiting highly motivated colleagues and post-graduate students against the risk that people may feel intimidated into volunteering in order to be seen as co-operative. This may be particularly problematical when students are looking for employment or staff for promotion. It is therefore probably best to avoid using people who are in anyway associated with the project or who have a working relationship with members of the team, thus excluding all those in the same group and possibly within the same department or even institution. This has to be a matter of judgement within each organization.

Another way in which volunteers may feel pressurised into joining a study is if they are approached directly by a friend or person senior to them. To avoid the need for a direct approach advertisements can be placed in strategic places, appropriate to the study, such as at the host institute, local doctors, supermarkets or at other organizations where there are likely to be a reasonable number of people in the target group. Advertisements, or articles about the study, can also be placed in local papers or those providing support for people with a particular problem, *e.g.* a newsletter for people with inflammatory bowel disease, or the study might be discussed on local radio. It is also possible to build up a database of people interested in volunteering for studies in general, and use their demographic details to send out targeted letters (such a list is subject to data protection legislation). Whatever approach is chosen, the method of recruitment is an important ethical aspect of a study, so advertisements and other plans should be subject to ethical review prior to use, making it clear where they will be placed and of course permission must be sought from the appropriate authorities at any organization involved prior to any recruitment campaign.

It is well accepted that when dealing with healthy volunteers, where the study is unlikely to provide any direct benefit to the individual, an "inconvenience" payment is appropriate. However, the payment must not act as an inducement to participate but only to recompense for the inconvenience and discomfort associated with the study. If we assume it is fair that all participants get paid the same then judging how much to pay is difficult, as what might seem a high payment to a student may seem derisory to a wealthy business man. The amount offered should be agreed with the ethics committee and perhaps a standard rate for all studies agreed for commonly used procedures such as phlebotomy.

Although a direct approach to individuals asking them to act as healthy volunteers is not desirable, recruitment of patients may on occasion only be feasible by direct approach but this should be avoided whenever possible. It is preferable that a letter explaining the study should be sent out to people prior to their next visit to the clinic or inviting them to a special session. Data protection rules may mean that access to the names and addresses of a group of patients is limited so a scientist may have to ask the doctor to send out an agreed letter to all relevant patients asking them to contact the investigator if they are interested in participating in a study. In responding to the investigator they are releasing their details, which must then be treated as highly confidential, as is the case for all participant information. When recruiting patients it is not acceptable to suggest they might be able get treatment more quickly by participating in the study as this would be considered an unacceptable inducements in the same manner as excessive financial payments. Occasionally free health checks are given as an inducement to participate in a study and on occasion this may be appropriate, *e.g.* giving feedback on plasma cholesterol levels, but this must be done by an appropriately trained person who can ensure the correct advice is given to the participant. It is generally not useful to give individuals their personal data as it has no specific clinical value and will probably be meaningless outside the context of the whole study.

The numbers of people to be recruited also constitutes a major concern for an ethics committee. Too few individuals may mean those involved are highly inconvenienced without any statistically meaningful results being produced. At the same time it is unethical to study more people than are required to get a statistically and clinically or scientifically significant result. To this effect it is required that power calculations are undertaken preferably with advice from a trained statistician. Good advice on the calculation of numbers is available within a number of text books [Altman, 1991]. These calculations require the investigator to have an idea of the variance associated with the most critical end point. This might be taken from previous pilot studies or from the literature. The calculations also require an estimate of what change is really meaningful in terms of a scientific or clinical outcome. Are we expecting a 10% or 25% drop to really convince ourselves the difference is important?

THE CONSENT PROCESS AND INFORMATION SHEET

Once a potential participant has been recruited they must give their fully informed consent to the study. In British law consent has a legal status and cannot be given by children or certain categories of adults such as those with severe learning difficulties. Children should however have studies fully explained to them and their assent obtained as well as the consent of a parent or legal guardian. The researcher must be sensitive to the level of understanding of all volunteers such that some might require in depth discussion of the science while others need only understand at a more superficial level why the study is being done and how it will affect them. Generally once someone has volunteered to participate

TABLE 2. A question and answer type format for information sheets given out to prospective participants for a generic phytochemical bioavailability project. The suggested answers provided here would have to be made more specific to individual projects and to be preceded by an invitation paragraph. The information sheet would be produced on headed writing paper.

Question	Prototype Answer
What is the purpose of the study?	It is known that people who eat a lot of fruit and vegetables have a lower risk of getting a number of diseases associated with old age. One possible reason is these foods contain large quantities of phenolic compounds. Studies using cells grown in the laboratory tell us how these compounds may work but we do not know how well some of them are taken up into the body and what concentrations are found in the blood. Therefore the aim of the study is to feed these compounds either as foods or in an isolated form in a capsule.
Why have I been chosen?	You have been chosen because you have expressed an interest in the study in response to an advertisement or letter and are aged between 18-45.
Do I have to take part?	Even though you have responded you do not have to take part and if you do take part you can drop out of the study at any stage.
What will happen to me if I take part?	If you do chose to take part we will first ask you to come to The Institute and explain the study to you in more detail which will give you the opportunity to ask any questions you might have. If you are still interested we will invite you back at a mutually agreed time when we will ask you to sign a consent form and ask some questions about your general health and take a blood test and urine test to check that all the measurements we are interested in are normal. Your blood test results will be sent to your doctor. You will need to avoid eating for 10 hours prior to the test but you will then be given breakfast. (All food is produced to the highest hygiene standards and the capsule produced in a specialised laboratory). If all your tests are OK we will ask you back on three occasions to eat a meal containing either raw or cooked vegetables or to take a capsule containing particular phenolic compounds (x,y & z). The research nurse will then place a thin plastic tube into a vein on your arm so we can take several blood samples during the day. We will not take more than a total of 150mls (equivalent to a small cup) of blood on each occasion. The blood samples will then be used to measure how much of each phenolic compound has got into your blood and how long it remains in the blood.
What are the possible disadvantages of taking part?	There are no serious disadvantages in taking part in the study apart from the time you are giving us. The time for each full study day will be approximately 6h at The Institute. There is a very small risk that you might have a small bruise following the placement of the tube in your arm.
What are the possible benefits of taking part?	There are unlikely to be any direct benefit to yourself but the results of the study will help us to understand more about how fruits and vegetables help prevent disease.
What if something goes wrong?	This study is being sponsored by the food company XXXXXX and in the unlikely event that any problems arise as a result of your taking part in the study they are fully insured.
Will my taking part in this study be kept confidential?	Yes. All samples are coded and even you will not be told your own individual results. However, at the end of the study you will be told the main conclusions from the study. The only results that you will be made aware of are any of the screening tests showing results outside the normal range and then you will be advised to consult your doctor.
What will happen to the results of the study?	The results of the study will be published in a scientific journal and used to inform nutritional and health specialists. However no named results will be published so your input into the study will remain completely confidential.
Who is organising the research?	This research is part of Mr/Ms XXXXXX PhD project at XXXXXX Institute and is funded by XXXXXX food company.
Who has reviewed the study?	The project has been reviewed by The XXXXXX Research Governance Committee and the XXXXXX Human Research Ethics Committee.
Contact for further information	Insert here names - phone numbers, *etc.*

they must be given a written information sheet, possibly including drawings and diagrams, designed to provide them with all the essential information required to give fully informed consent. This should be written in a language they are fluent in and at an appropriate reading age and if dealing with people likely to have reading difficulties large print should be considered. This should then be followed up with a verbal discussion providing an opportunity to demonstrate procedures, answer questions and clarify details. In the recent guidelines issued by the Department of Health for England and Wales [Dept. of Health for England and Wales] it is suggested that the information sheet is set out as a series of potential questions which the researcher provides answers to. At the start of the information sheet there should be a short paragraph inviting the reader to participate in a study and briefly explaining why it is important. A modified version of the questions suggested and some typical answers used in a generic phytochemical intervention study is shown in Table 2. On occasion there may be a conflict of interest between undertaking good science and fully informing participants. For example by telling participants that a particular group of foods may have beneficial properties you may encourage them to eat those foods. If this happens in your control group this might compromise the science. Therefore it may be appropriate to only partially reveal details of the science to the participants but this should be brought to the attention of the ethics committee so they can judge whether such an approach is acceptable.

Once a full explanation of the study has been given the volunteers should preferably be given at least three days to think about the study before signing a consent form. In many studies the next step will be to assess whether people fit within the inclusion criteria, including taking a screening blood sample, so it is often convenient to invite them back a few days later when they will sign the consent form and then have a first blood sample taken and be questioned in relation to their general health. The consent form should be on paper which is clearly representing the institutions involved in the study, using logo's *etc*., and include the title of the study, a clear statement that participants can withdraw from the study at any time without explaining why, and the names and signatures of the participant, person who has explained the study and the principal investigator. The participant must be given a copy of both the consent form and patient information sheet to take away with them as well as any supplementary detailed information such as personalised study timetables.

GENETIC SCREENING

In an intervention study looking at nutrient-gene interactions there may be a need to analyse for genetic polymorphisms. Other studies rely on looking at baseline levels and changes in gene expression at the RNA level which currently do not attract particular concern. Screening for polymorphisms at the DNA level which reflect germ line inheritable differences will be discussed at length during the ethical review process [Human tissue in biological samples...], and possibly involve referred to national level committees while changes in a DNA in cancerous tissue pose few problems. However, these differences must be clearly explained to participants as part of the process of obtaining informed consent. The use to which any genetic information is put must be very carefully considered. If there is no known treatment for a genetic condition then it is generally appropriate to do all analysis on fully anonymised samples. It is currently agreed in the UK that this type of analysis does not need to be revealed in relation to any application for insurance. The question of giving feedback on samples where there might be some treatment for the condition becomes more difficult. For example, is it acceptable not to tell someone they are homozygous for the HFE (haemochromatosis) gene? There is fairly low penetrance of this gene, in terms of iron overload, but advice to reduce iron intake and monitoring iron status would be appropriate and if necessary initiation of phlebotomy to reduce risk. To make a decision of this kind those involved need to consider resources available locally in terms of genetic counselling and monitoring of iron status. Genes with higher penetrance such those associated with familial hypercholesterolaemia present less of a dilemma as members of a family with these genes are likely to be aware that they may carry a genetic trait and they may be actively seeking this information and as there are also effective treatments for the condition the information is useful to them. Once again, the participant should have access to genetic counselling in making a decision as to whether they want to know their results and whether they should participate in the study. However, if the mutation is related to only one gene in many being studied as part of a large investigation it may not be practical to give this level of in put and once again the investigator is best advised to do all screening anonymously and high risk individuals seek advice through their own doctor.

INCONVENIENCE TO, AND SAFETY OF PARTICIPANTS

When conducting an ethical review the members of the committee must make a judgement as to whether a study should be approved based on the level of intrusion into the persons life or even possible risk compared to the benefits. Although this judgement is ultimately up to the individual the members of the committee are asked to make an informed decision before participants are even approached and to check all information has been included. The committee members will look for whether staff are properly trained in the procedures to be undertaken, *i.e.* cannulation, phlebotomy, collection of biopsy samples, communicating with non-scientists, collection of questionnaire data *etc*. They will also judge whether the time put in by participants is acceptable considering the potential benefit of the science. With more fundamental science this would be considered in relation to novelty rather than anticipated clinical benefits and less risk would be considered acceptable. When considering giving a chemical extracted from a food information on effects, doses *etc.* in animal studies would be required as well as a comparison between the amount normally eaten and those being given in a study. If an enriched supplement or isolated food ingredient is to be given the committee will need to be shown that this is to be produced at food grade levels, not just in a normal research laboratory and any food produced cooked in proper kitchens to a standard equivalent to those expected from commercial food outlets. Consideration of the bioavailability of isolated chemicals compared to that when present in a whole food must be taken into account in making dose comparisons as should the actual chemical form it is being given in.

For some studies it is necessary to introduce samples intravenously. If this is to be done the sample needs to be produced to pharmaceutical standards in specialised laboratories and kept sterile until use. For example some studies require the introduction of a labelled compound into the blood. Usually this is done with stable isotopes which are presumed radiologically safe, but participants must have this clearly explained to them and scientists cannot use the excuse "it is too hard too explain and there will be a recruitment problem". In some cases radioisotopes are used in a study. In this situation the ethics committee would seek advice from the local radiation protection officers and the information sheet must make a comparison to background radiation levels or dental X-rays. A similar comparison might have to be made if X-rays are to be used to measure an end point or positioning of a tube *etc*.

Taking of samples for analysis may present issues of safety but scientists should also be aware of personal sensitivities over collection of samples such as urine, faeces or menstrual blood losses. In terms of physical safety access to facilities for normal personal hygiene combined with well designed collection techniques should overcome possible microbiological hazards and taking care not to take excess venous blood during a study will avoid issues associated with low haemoglobin levels. It would be generally recommended that volunteers should not be anaemic at the start of the

study, unless that is a requirement of the study. Then only blood sampling up to the amounts used when donating blood for medical purposes can be considered acceptable. The actual amount required will be dependent on the study design and while it is unacceptable to take considerably more than is required for the planned assays it is also sensible and ethically proper to take enough to repeat samples should a problem arise during analysis, as long as this is achievable within the total allowable donation, which in the UK is 475 mL within a three month period.

DATA PROTECTION IN RELATION TO AN INDIVIDUALS RESULTS

Protection of an individuals data is an important aspect of Human Rights legislation in the European Union [Directive 95/46/EC] and in all countries data protection laws will govern how a study can be conducted [Personal information..., 2003]. No personalised data should reach the public domain without specific consent even to the extent that participation in a study is confidential. Access to medical lists is restricted and generally people from outside an organisation should not have this access without prior consent of all those on the list. This means that recruitment from a medical list must be made through the health service personnel rather than a list being handed over to the scientist. Once people have volunteered, their personal data should be kept in a secure place and all analysis under taken on coded samples. Initial health screening will however have to be linked to the individual so that they can be told if they fit the inclusion criteria. This data should be held by as few people as possible and the ethics committee should know who has access to this data. It is usually the investigators listed on the proposal form plus a research nurse or study manager.

Informing people why they have been excluded from a study requires some consideration. For example, a blood screening test for liver function, lipoprotein profiles and markers of tissue damage and blood counts may have been deemed necessary for a particular study and some of these values fall outside the normal range. In a non-clinical environment it may be difficult to conclude whether these are important and the scientist is not trained to interpret these results for participants. However it would be unethical just to tell people they are not eligible for the study. One suggested solution is to obtain the services of an interested clinician who can recommend what to do, *i.e.* get a retest because the person was probably suffering from a virus at the time of sampling or perhaps forgot to avoid alcohol prior to testing. If, however, on retest, the samples are still outside the 'normal' range then the participants personal physician (General Practitioner or GP in the UK) should be informed. At The Institute of Food Research our current practice is to inform participants that their results were outside the 'normal' range and so they will not be suitable for the study and they should discuss their results with their doctor. A variable degree of urgency may be associated with this advice based on the interpretation provided by the advising clinician. We now send all screening results to the volunteers doctor along with an explanation of the study. It is therefore imperative that participants know their doctor will be sent this information and they should sign an agreement to this effect as part of the consent process. This process is unlikely to be necessary if working with patients under the supervision of a consultant although it is probably still good practice to advise the GP, but through the consultant you are working with.

Other data collected from the study should be anonymised and then can be stored for future use. If this is to happen then the wording of the information sheet should not exclude this possibility or further consent for follow on studies will be required by the ethics committee. However, in the case of tape or video recordings it is not feasible to anonymise the data so the tapes must be destroyed at the end of the study as defined in the information sheet.

STORAGE AND DISPOSAL OF SAMPLES

Although a scientist will have a specific study in mind when collecting samples it may be felt that samples could be used in future studies. This is particularly likely to arise if spare blood has been collected and then analysis has been trouble free. In prospective studies blood samples will have been taken and stored for long term analysis and novel methodologies will develop with time, which can later be applied to those samples. In either situation it is best to anticipate that this might happen and ask participants permission at the start to keep their samples in long term storage for future analysis. It is probably appropriate to get consent for this as a specific point on the consent form. There is a particular sensitivity in this respect over DNA analysis and if genetic screening is to be undertaken in the future specific reference to this should be made in the information sheet. The ethics committee will need to see good supporting documentation that this analysis will be undertaken on fully anonymised samples, employing a double coding technique to prevent results being returned to the participant.

DISSEMINATION OF RESULTS

At the end of the study it is desirable that volunteers get feedback from the study as well as a letter of thanks. The feedback is not normally specific to them but they can see how their input has helped in a scientific achievement. Volunteers are normally very pleased to have been of help and the feedback means they are more likely to volunteer for another study. It is preferable that results from a study are published in the scientific literature as soon as possible although sponsoring companies might wish to with-hold publication. This is acceptable assuming eventual publication is likely and that the possibility of delayed publication or production of a confidential report is highlighted from the start. Whenever appropriate it is also desirable to publicise results to a wider audience using technical journals, magazines, newspapers and other media tools. When doing this the results should be put in context with wider health issues and care must be taken to avoid scare stories. Handling the media requires specific skills.

FEEDBACK TO THE ETHICS COMMITTEE

During the study those involved in dealing with volunteers are required to record any problems encountered by the volunteers whether they are associated with the study or not. So for example if a person on a vitamin intervention study breaks a finger playing football this must be reported as an

adverse event. If the event is considered, by the advising clinician, to be in any way potentially linked to the study then the adverse event should be reported to the Chair of the Ethics Committee as soon as possible as the ethics committee will have to decide whether the study should proceed or be stopped or possibly modified. It is also a requirement that end of year and end of study reports are sent to the committee outlining numbers of participants recruited and any changes in personnel with a peripheral role in the study. Changes in key people running the study with access to named data or in contact with the participants should be reported as and when they happen.

CONCLUSION

Although historically, nutritional intervention studies have not been seen to require the same degree of ethical considera-tion as pharmaceutical trials, attitudes have changed and appreciation of the issues of concern have increased in recent years. This is now reflected in the requirement by journals for authors to show that human studies have been reviewed by a properly constituted research ethics committee. This committee will focus on an assessment of the risk, discomfort or inconvenience to the volunteer as compared to the value of the research. In the vast majority of nutritional studies it is ultimately the individual volunteering for the study who makes a choice as to whether to participate and so the ethics committee must ensure she (he) has all necessary information about the study so an informed choice can be made. There-fore the information sheet and consent form provide a major focus for ethical review while the safety of the research subject and the scientific value of the research are also of great importance.

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