

Ethics of studies involving human volunteers. II. Relevance and practical implementation for cosmetic scientists

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Synopsis

The importance to the personal products industry of testing novel products in healthy human volunteers and the need to ensure the trials were both safe and ethical were addressed in Part I. The historical development of ethical standards for human testing was also summarized. The present paper highlights the ethical principles to be considered when testing novel *non-medicinal* products on human volunteers, and it describes how they can be implemented in a pragmatic manner to avoid delay to the sponsor's research program. The structure and function of ethics committees is discussed.

INTRODUCTION

Part I provided a brief overview of the history of the ethics of medical research on humans (1). The present paper discusses implications and implementation for non-medical research. The principles that flow from the historical review detailed in Part I may be described as a set of ethical norms that provide a framework for the decision process by which proposals for research with healthy human volunteers may be reviewed. They embrace:

(a) *Autonomy*. The principle of autonomy holds that the individual is free to make choices and is self-governing. This right of individuals to decide their own course of action is a key pillar of modern ethical codes and includes maintaining volunteer confidentiality and obtaining informed consent.

- Confidentiality. Autonomy also provides individuals with the right to control access to information about themselves and for it to be shared only on a "need to know basis" for professional purposes. The control over disclosure is an important responsibility for the researcher.
- Informed consent. Volunteers must give their consent to the research process after being given a full explanation of the experiment, its risk, and potential benefits (if any). It is also incumbent upon the investigator to ensure the volunteer is capable of making an informed decision, i.e., be able to receive the relevant information, retain it, process it, and formulate a decision. Consideration should be given to the vulner-

able, e.g., children and those with severe mental or behavioral disorders and persons unfamiliar with medical concepts and technology. There should be no coercion, undue influence, or intimidation to take part. This point is particularly relevant when volunteers include co-workers, students, prisoners, or members of the military. Similarly, there should be no excessive inducement to take part: the level of remuneration (if any) should reflect the inconvenience to the volunteer during the trial and reimburse any out-of-pocket expenses. Payments should not be used to engage volunteers in studies that they would not normally take part in simply to benefit from a substantial monetary reward. Once accepted onto a study, subjects should also be given the right to withdraw at any time from the study if they so wish.

(b) *Beneficence and non-maleficence.* These essentially provide for the experimenter to seek only to do good and to explicitly do no harm. Within the field of medical research, arguments for these principles can be made for much of the work carried out. However, they can be difficult if the research participant does not benefit directly, e.g.,

- in safety studies on medicines using healthy volunteers, or
- because of the long delay between obtaining results from basic clinical research and commercial exploitation, or
- if the study did not provide a positive result, or
- if the trial was conducted purely as an educational program for practitioners.

The arguments are even more difficult to substantiate in the cosmetics arena, where the benefits to the individual and society as a whole are less easy to justify. It is therefore incumbent upon experimenters to carry out a risk-benefit analysis to justify to themselves and to an ethics committee that the proposed study's benefits outweigh the potential risks to the participants. This should include a review of the scientific validity of the study, since research that is flawed will present no benefit to either the subject or society and cannot be ethically valid. Furthermore, poorly designed studies could affect the risk-benefit analysis and may even prove to be positively harmful to volunteer participants.

(c) *Justice.* The principle of justice requires the burden of research to be distributed fairly, i.e., the group that will benefit from the research should be the group on which the research is carried out. This prevents the abuse of disenfranchised bodies of society, e.g., the export of research to developing nations. Obviously, there is a scientific drive to ensure the test population closely reflects the target population. Also, a researcher who has clinical or teaching responsibilities might be accused of neglecting these daily duties in the event of conducting excessive research.

While these ethical principles are not exhaustive, and their relative weight may vary between societies, they provide a set of core values against which the researcher and the ethics committee (as guardian of these principles) should measure their work. But what of the relevance to the cosmetic scientist?

The chemical, cosmetic, toiletry, detergent, household cleaning, and food sectors conduct extensive human testing on healthy volunteers to evaluate the quantitative and qualitative effects of chemical, physical, biological, and radiological agents. Work is conducted in academia, in industry, and by independent commercial contract clinical research organizations. A selection of common routine, non-medical, healthy human volunteer tests is presented in Table I. These human studies must be conducted safely and ethically to protect the health and well-being of the volunteers. Drivers are illustrated by Table II.

Table I
Selected Examples of Non-Medicinal Healthy Human Volunteer Studies

<u>Hair</u>	<u>Skin</u>
Anti-dandruff	48/96-hr patch testing
Hair clipping for <i>in vitro</i> analysis	Arm immersion tests
Hair volume salon half-head studies	Ballistometer tests
	Biopsy
	Comedogenicity
	Cumulative irritation
	Exaggerated use
	Flex-wash tests
	Hot-room antiperspirant studies (antiperspirants and deodorants)
	In-use safety
	Itch testing
	Ocular irritation
	Photosensitivity
	Phototoxicity
	Repeated-insult patch testing
	Soap-chamber tests
	Tape-stripping
	Transepidermal water loss (corneometer readings; evaporimeter studies)
	Underarm sniff tests

Table II
Reasons for Growing Concern for Subjects in Healthy Human Volunteer Trials

- The duty of care owed to volunteers by the management of companies/institutions conducting and sponsoring such research.
- Risk/benefit analysis for volunteers that indicates that while the risks are much lower than in the more-regulated research trials on medicines, the potential health benefits to individual research participants are less clear-cut, and usually non-existent. The benefits tend to be to the success of the business and to future consumers as a whole.
- Some testing regimes may be invasive.
- Trends to develop products with more physiological claims such as in cosmeceuticals, functional foods, and the need to provide clinical evidence to support marketing claims.
- A common practice of using employees as trial subjects and the potential for coercion by management for staff to participate (their involvement must be truly voluntary), or for subjects to be overused or recruited onto different trials simultaneously.
- The trend for journal editors to seek confirmation from authors that the "clinical" studies have been conducted to GCP and have been subjected to ethical review before papers are accepted for publication.
- The need to ensure the continued acceptance of this type of testing by the general population.
- The need to provide protection for the scientific staff and institutions involved in human testing in an increasingly litigious environment.

The Royal College of Physicians has suggested (2) that the same general principles of ethics used for medical studies be extended to non-medicinal human research. Thus,

Naturally, it is in medical research that this College has most expertise . . . but the general principles of ethical review have wider application. The College believes that authorities which appoint Research Ethics Committees serving non-medical areas will profit from this guide to ethical review of medical research. They will adapt the membership of any Committee they appoint according to the class of studies to be undertaken.

In a report on research on healthy volunteers, the same College stated (3) that "Cosmetic and other substances, e.g. domestic washing powders, used on or by man, may need to be tested on healthy human volunteers and so come within the scope of this Report."

EU rules governing testing of cosmetic ingredients and finished products requires adoption of the World Medical Association Declaration of Helsinki and the EU Directive on GCP for Trials on Medicinal Products, for protocols to be submitted to an authorized ethics committee, and for trials to be conducted and monitored under the direction of suitably trained personnel.

The Royal Society of Chemistry issued guidance (4) to members who could be involved professionally, or as potential volunteers, in healthy human volunteer experiments. Advice included submission of test proposals to a research ethics committee. The professional and ethical elements of market research are covered in a Code of Conduct (5).

IMPLEMENTATION OF ETHICAL REVIEW

Since the ethical review of studies of non-medicinal products in healthy volunteers is currently not regulated, there is some flexibility in how the general principles are applied in a pragmatic manner to match the needs to product sector, while protecting the trial subjects. However, it is clear that this research must conform to international guidelines and that investigators should not be the sole judge of whether their work complies with such standards.

RESEARCH ETHICS COMMITTEES (RECS)

In theory, investigators could submit proposals for healthy human volunteer trials to existing, recognized, independent RECs/IRBs. Some, though not all, of these RECs are formally recognized for review of Phase 1 trials on healthy volunteers, but European legislation as it applies specifically to these committees is currently in flux. In the UK these RECs are government-funded to provide ethical review of trials on *medicinal products* only, and at no cost to the drug industry. Depending on workload and interpretation of the regulations, these committees may vary in their willingness to undertake reviews of non-medicinal trials. The applicant would need to arrange separate funding arrangements with the committee.

Alternatively, sponsors could submit proposals for review by fully independent but not government-recognized RECs, e.g., those established by contract research organizations.

Sponsor companies could also set up their own RECs, though clearly this would be perceived to be even less independent. To minimize the opportunity for sponsor influence on an internal REC, the committee could comprise only external members empowered to appoint (and dismiss) the chairperson. A less-transparent arrangement is to staff the committee with a mixture of external members and internal employees. The latter must at least be independent of the staff and reporting-line of those conducting the trials under review. Criticism could include the opportunity for covert or overt management pressure on staff members to provide a favorable review. Ideally the Chair should be an external member. The sponsor company should arrange indemnity for external members. The approach of one multi-national has been described elsewhere (6).

MEMBERSHIP ● F RECS

REC membership should be balanced for age, gender, and lay/expert background. The size of the quorum, e.g., 5–7 (to include at least one lay and one expert member), should first be agreed upon, and then the committee size defined to ensure a minimum quorum for any meeting. Typically, the REC may comprise 10 to 18 members maximum. As a guide, at least one third should be lay.

●FFICERS

A decision must be reached on how the Chair and Vice-chair should be elected. This may be an appointment by the authorizing authority or election by and from within the REC members. A secretary or administrator is required to arrange the meetings, take minutes, maintain REC files/library, and interface with applicants, although written decisions of the committee on specific submissions should be signed by the Chair or Vice Chair.

FUNCTIONS

The aim of the REC is to provide independent advice to participants, researchers, sponsors, employees, and professionals on the extent to which proposals for studies on healthy human volunteers comply with recognized ethical standards, and to approve, require amendment, or reject studies submitted to it. Its prime responsibility is to protect the dignity, rights, safety, and mental and physical well-being of potential or actual research subjects. Concern over the volunteer must prevail over the interests of science or society. A secondary responsibility is the protection of researchers and institutions where any matter of an ethical nature might affect them, provided that the interests of the trial volunteers take priority.

The scientific robustness of submissions for ethical review should have received prior, separate peer review. While safety and science quality are not the direct responsibility of the REC, it is advisable for the committee to become familiar with the salient ethical components of each type of test that it reviews, including any potential risks to volunteers. For example,

- Transepidermal water loss measurements are affected by race, gender, site of application, and emotional state of the test subject. Experimental design is crucial, and studies should be carried out in a controlled environment at a standard temperature and relative humidity, with time allowed for subjects to reach equilibrium before each assessment is made.
- Ethical considerations for compatibility testing of finished cosmetic products in healthy human volunteers are highlighted in Table III (7).
- Tests should not cause irreversible damage. Trials on products containing ingredients known to be teratogenic (e.g., in animal studies), depending on safety margins, may need to be restricted to males or post-menopausal women.

The committee may require ongoing review and will need to be kept informed of adverse and seriously adverse events and ensure that these are followed through to resolution. Depending upon the type of product being studied and the type of tests undertaken, common potential adverse effects include skin or eye irritation, itching, contact allergy, contact urticaria, pigment changes, hair and nail changes, and subjective symptoms.

Table III.

Recommended Ethical Considerations for Compatibility Testing of Finished Cosmetic Products in Healthy Human Volunteers (after ref. 7)

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- Not a substitute for animal testing.
 - Performed only to confirm, in a limited number of subjects, that products do not damage skin and mucous membrane, as already expected from other sources.
 - Before the trial commences the study supervisor must possess product formulation, pre-clinical safety assessment, its conditions of use, and any warnings.
 - Protocols should be based on sound science and potential risks. Even if no risks are associated with the work, the studies must not be conducted if they do not comply with scientific criteria.
 - Tests should not be performed unless the importance of the objective is in proportion to the inherent risks to the subject.
 - The study must cease as soon as any risk outweighs the potential benefit of the trial.
 - Skin compatibility testing should only be carried out by technically qualified persons under medical supervision.
 - While acceptability tests in consumers do *not* need review by an REC, compatibility test protocols possibly posing a risk to volunteers *should* be submitted to an REC for review.
 - Volunteers are adequately informed of the aims, methods, and potential risks/discomfort, and give their free written consent before being recruited.
 - Subjects with current dermatitis or who know of past allergic contact dermatitis related to the ingredients should be excluded.
 - Pregnant or lactating females should be excluded, except in very special listed circumstances.
 - Children should be excluded, except in very limited identified circumstances when their own free informed consent should be obtained in addition to that of their parent or guardian.
 - Study reports should include all experimental details to provide a rationale of the trial and to preserve the accuracy of the results.
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The sourcing of human tissues and other samples from, e.g., hospitals, universities, and commercial establishments for industrial research should also be considered by a REC. These samples are often supplied by patients as part of their medical treatment, e.g., for routine clinical testing or donated through local health services and then sold for research usually without the patient's awareness. Researchers should be able to confirm that their supplier has the necessary consents. From 2006, UK law relating to collection, storage, and use of human samples in research will be tightened by implementation of the Human Tissue Act 2004 (8), which addresses informed-consent and ethical review (9).

The Committee should issue an annual report to the "appointing authority," and for internal committees, this should be sent to the most senior manager, e.g., Director of Research or Managing Director.

The REC administrator should hold on file CVs for each member and record any relevant training that they receive. Induction training for new members should include background and history to RECs, their role within the organization, the REC constitution, implementation of REC SOPs, and overview of the types of healthy human volunteer studies routinely submitted. Ongoing training in more specialized elements should be provided as required.

MEETINGS

Meetings should be arranged to meet demand, and proceedings should be documented. Minutes should not link individual members to comments. They should be copied to

members, but it is arguable whether minutes should receive wider distribution (see Confidentiality, below).

Sufficient time should be allowed for members to study applications prior to meetings. The meeting should reach unanimous decisions by consensus wherever possible. Where a consensus is not achievable, a formal vote should be taken based on a one-member one-vote principle. Expedited reviews by post should be reserved for the most simple applications; they should be the exception rather than the rule. Reasons for deferment or rejection should be clearly stated. The committee should notify applicants of its decisions in writing as soon as possible after the meeting.

CONFIDENTIALITY

All business of the committee should be conducted in private to preserve confidentiality, and documentation related to the committee and its meetings should be confidential so as to encourage full and frank debate. When applicants attend meetings to present their proposals and answer questions, they should be requested to leave while the committee formulates its response. They will not be permitted to take part in voting. Similarly, the confidentiality of data relating to individual trial volunteers (medical history, compensation, adverse events) should be ensured.

FINANCIAL

The committee should be provided with facilities, administration assistance, and an annual budget from its appointing authority to cover training, site visits, etc. In addition, consideration should be given to awarding external members an honorarium to cover their travel expenses, loss of earnings, and time preparing for, and attending, meetings.

REC PROCEDURES

The REC should have a constitution and portfolio of SOPs describing its modus operandi.

ETHICS REVIEW DOCUMENTATION

Applications could mirror the documentation required for ethical review of trials on medicinal products. This is good practice for true clinical studies but is likely to be over burdensome for more routine, low-risk studies such as hot-room sittings, sensory studies, patch testing, and flavor trials. For routine tests that conform to a general pattern using substances recognized to be safe, SOPs could be submitted for generic review by the REC. These should contain

- a description of the methodology
- the definition of expected adverse reactions (e.g., irritation levels)
- the nature of products to be tested (i.e., comprising standard ingredients)
- the decisions and justification for prior assessment of safety
- means of monitoring for adverse reactions
- the subject information sheet and consent form

For high-throughput routine studies, quality control measures are required to monitor the studies periodically in order to

- provide the REC with assurance of compliance with agreed procedures,
- identify areas for further improvement,
- confirm that the system is not abused, and
- check that volunteers are not being “over used.”

A report of the number of tests conducted and the number of adverse events should be reviewed periodically. Serious adverse events must be reported to the chairman within three working days and followed through to completion. These must be discussed at the next REC meeting to permit members to reconsider the status of their generic approval.

Trials should be submitted for ethical review on a case-by-case basis if they involve

- “proof of principle studies”
- novel or non-routine protocols
- products containing novel ingredients
- products that have previously caused harm and have since been modified
- minors

Other documents reviewed by the REC should include safety data sheets, panelist information sheets and consent forms, “case-report forms” to record trial data, questionnaires including confidential medical questionnaires, and recruitment advertisements. Issues considered by a committee in preparing its opinion will include those listed in Table IV.

The REC/IRB should be cognizant of sponsor deadlines and strive to provide a service that does not delay the start of studies, although clearly the sponsors must also be realistic in their expectations. For regulatory studies, applications for, e.g., clinical trial authorizations can proceed in parallel with application for ethical support, but these trials, if on medicinal products, must be reviewed by a recognized REC.

Table IV
Examples of Factors Considered by Research Ethics Committees

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- The relevance of the study, its aims and design.
 - The benefits versus the risks.
 - The suitability of the researchers (review of investigator CV); availability of medical support/supervision during the trial and aftercare and the rights to terminate the study; scientific responsibilities for preparation, dosage control, and quality assurance of product and analysis of samples.
 - The safety of the products including purity, and the properties of likely contaminants/additives, and evidence to confirm minimal risk to subjects.
 - The suitability of the facilities for the trial (by visiting the test facility if necessary).
 - The arrangements for recruiting subjects (informed consent, inclusion/exclusion criteria).
 - The special requirements for recruiting minors, volunteers whose first language is not English, etc.
 - Medical histories and degree of supervision during, and after, exposure.
 - The means of identifying, recording, and investigating adverse events.
 - The amounts of, and the arrangements for, rewards to volunteers and external investigators, and compensation to subjects who are injured (e.g., “No Fault” compensation).
 - Mechanisms to prevent overuse of individual volunteers.
 - Documentation (records, reports, security, archiving).
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CONCLUSION

While proposals for biomedical research programs have been subject to ethical review for many years, regulation of non-medical human studies has tended not to provide an ethics focus. Nevertheless, there are moral and business reasons to seek independent ethics review of *all* healthy volunteer studies irrespective of the nature of the test protocol and product area. Sufficient codes and guidance exist to enable the basic principles to be identified and applied in a pragmatic manner, thereby assuring the safety and well-being of trial volunteers. By proper planning and professional project management, the process of seeking ethical review need not cause delays in the development program.

REFERENCES

- (1) P. A. Carson and J. Holt, Ethics of studies involving human volunteers: I. Historical background, *J. Cosmet. Sci.*, 57, 215–221 (2006).
- (2) *Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects* (Royal College of Physicians, London, 1990).
- (3) Working Party on Research on Healthy Volunteers, *J. Royal Coll. Phys.* 20(4), 1 (1986).
- (4) *Professional Brief: Guidance for Members Involved with "Healthy Human Volunteer Experiments"* (The Royal Society of Chemistry, London, 1994).
- (5) *Code of Conduct*, The Market Research Society/Industrial Marketing Research Association.
- (6) J. H. Steadman, Ethical review of human experimentation in the consumer products industry, *Neth. J. Med.*, 52, 138–141 (1998).
- (7) European Commission, *The Rules Governing Cosmetic Products in the European Union, Volume 3: Guidelines (Cosmetic Products)* (Annex 11 and 12, 1999).
- (8) *The Human Tissue Act, 2004*, Chapter 30 (HMSO, London, 2004).
- (9) P. A. Carson, J. Holt, and M. McGrady, The ethical impact of the UK Human Tissue Act for the foods, cosmetics, toiletries and detergents industries, *Res. Ethics Rev.*, 2(1), 10–14 (2006).