Introduction of New Devices
Workshop 3
Monday, 23 August, 2010 0900-1200

Time	Time	Topic	Speaker
0900	0905	Introduction	Andrew Farkas
0905	0935	Introduction of new devices – ethical considerations	Cathryn Glazener
0935	1005	Clinical data and EU Regulation of Medical Devices	Paul Brooks
1005	1035	Ethical and practical considerations of conducting a trial of new devices	Paul Hilton
1035	1105	Break	
1105	1200	Panel discussion including members of ICS Ethics Committee	

Aims of course/workshop

The purpose of this workshop is to consider the ethical dimension of introduction of new devices in the context of clinical and regulatory requirements. The instigation of meshes and tapes has brought benefits to pelvic floor surgery and continence care but raised many ethical issues. These include the ethical imperative to test new devices with RCTs before clinical introduction and the validity of other means of monitoring success and complications, such as registries. The ethical responsibilities of manufacturers and potential bias in trials will be discussed. Ethical aspects of training will be considered, as will the funding of new devices. The regulatory framework and implications for globalisation of new devices will be addressed.

Educational Objectives

The purpose of this meeting is to consider the ethical dimension of introduction of new devices in the context of clinical and regulatory requirements. The instigation of meshes and tapes has brought benefits to pelvic floor surgery and continence care but raised many ethical issues. These include the ethical imperative to test new devices with RCTs before clinical introduction and the validity of other means of monitoring success and complications, such as registries. The ethical responsibilities of manufacturers and potential bias in trials will be discussed. Ethical aspects of training will be considered, as will the funding of new devices. The regulatory framework and implications for globalisation of new devices will be addressed.

Introduction of new devices – ethical considerations in running an RCT

Cathryn Glazener

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HSRU is funded by the Chief Scientist Office of the Scottish Government Health Directorates. The author accepts full responsibility for this talk.

Outline of considerations

- Ethical imperative to test new devices
- Whose responsibility is it?
  - Manufacturers
  - Regulatory authorities
  - Funders of service provision
  - Clinicians
  - Specialist societies
- How should they be tested? (RCTs)
- Which outcomes matter, and whose outcomes?
- Who should fund these trials?
- Who should (a) run; and (b) participate in the trial?

Whose interests?

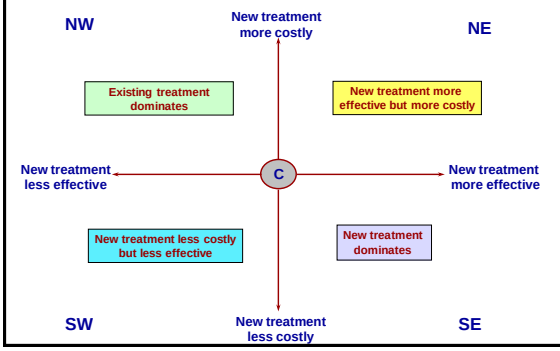
- Participants in (current) research
- Researchers (satisfaction, career)
- Patients who will benefit in the future
- Clinicians who will know how to treat their patients
- Health providers who will know what to provide
- Health service which will provide a cost effective service

Tension between current participants, future beneficiaries, science and society

Ethical imperative to perform research

- If the effects of a treatment are unknown it is ethically imperative to identify them
  - as it may not work
  - as it may be harmful
  - as another treatment may work better or be less harmful
- If a new treatment is devised, it is ethically imperative to find out if it is better (more efficacious) and more cost effective than the existing (gold standard) treatment

The cost-effectiveness plane



Ethical responsibility

- To all patients
  - Find most efficacious treatment
  - Find least harmful treatment
- To society
  - Find most cost-effective treatment
  - Balance between efficacy and harm and cost

Ethical responsibility to participants in trials

- First do no harm
- Protect life, health, privacy and dignity
- Consideration of their (own) welfare takes precedence over interests of science and society

BUT

- Best treatment is unknown
- Participant may receive best treatment by (random) chance – as it is unknown whether the original or the new technology is the best
- Difference between individual and society benefit

Motivation

- Researchers and clinicians
  - Satisfaction, altruism
  - Career, salary, promotion, reputation
  - Power
  - Other benefits?
- Participants
  - Satisfaction, reward from helping with research
  - Benefits of the (new) intervention
  - Risk from unknown efficacy and adverse effects

Motivation

- Manufacturers
  - Money (profits and risks)
  - Shareholders, increase in share price
  - Risk of legal problems / compensation if adverse effects result from device or research
- Funders of research (independent)
  - Altruism
  - Eventual introduction of cost effective device (or not)
  - Benefits to society / NHS

Trial design to reduce risk of bias

- Randomised controlled trial
  - Randomisation process compensates for unknown sources of bias
  - Prevents known sources of bias (selection of patients, allocation to treatment)
  - Gold standard
  - Requires sufficient sample size for reliability
- CONSORT statement conditions

Bias from clinicians

- Willingness to participate in research
  1. Unwilling to risk new intervention without evidence of efficacy and safety
  2. Convinced of benefit therefore unwilling to deny their patients the benefit
  3. In equipoise and committed to randomisation so that unbiased and generalisable answer can be found quickly

Learning curve bias

- If new technique is difficult, how long before a surgeon is competent?
- Training issues
  - Who trains the surgeons?
  - How long is enough?
  - Who decides when competence has been reached?
  - Whose standards, how defined and regulated?
  - Which patients?

Bias from funding / control of research

- Independent funders / researchers?
- Manufacturers?
- Who designs the trial?
- Who owns the data?
- Who analyses the data?
- Who chooses the outcomes to analyse?

Bias in outcomes

Whose outcomes?

- Participant / patient
- Clinician
- Health service provider
- Manufacturer

Patient outcomes

- 'Subjective'
  - Prolapse symptoms (SCD)
  - Urinary symptoms
  - Bowel symptoms
  - Sexual function symptoms
  - Pain, adverse effects
  - Reoperation
- Difficult to measure and standardise (?)

Clinician's outcomes

- 'Objective'
  - Prolapse stage (POP-Q)
  - UI measured on pad tests, observation
  - Need for further treatment
    - Pessary
    - Repeat prolapse surgery
    - Oestrogen
- Difficulty of relevance to patients

Health providers' outcomes

- Cost of (new) treatment vs old treatment
- Increase in efficacy / patient health
- At what increase in costs due to adverse effects?

Manufacturer's outcomes

- Increased sales
- Increased profits and share price
- Cost of assembling the evidence / complying with regulatory framework
- Cost of dealing with adverse effects
  - Due to device versus due to operation
  - Expected
  - Due to negligence or fault

Responsibilities of researchers

- To conduct scientifically sound research
- To disseminate the research
- To implement the findings

Clinical Data & EU Regulation of Medical Devices

Paul Brooks
Vice President BSI Healthcare Solutions

raising standards worldwide™

Our Mission

To ensure patient safety while supporting timely access to medical device technology globally.

To provide our customers thorough, responsive, predictable conformity assessments, evaluations and certifications that are recognized and accepted worldwide.

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Europe Medical Device Regulations

- Medical Devices are regulated under the European Medical Devices Directives
- Three Directives
  - Active Implantable Medical Devices Directive (AIMDD)
  - Medical Devices Directive (MDD)
  - In Vitro Diagnostics Directive (IVDD)

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Definitions

'clinical data' means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;

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Definitions

'placing on the market' means the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished;

'putting into service' means the stage at which a device has been made available to the final user as being ready for use on the Community market for the first time for its intended purpose;

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Placing Devices on the Market

Member States shall take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied and properly installed, maintained and used in accordance with their intended purpose.

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MDD

- MDD requires all medical devices intended for placing on the EU Market are affixed with CE Marking* once:
  - Device meets Essential Requirements
  - Technical Documentation is complied
  - Conformity Assessment is completed
  - Manufacturer signs Declaration of Conformity

** Excludes devices for special purposes (custom made and clinical investigation)*

Conformity Assessment

- Conformity Assessment:
  - Quality Assurance Assessment (GMP) ISO 13485
  - Product Evaluation (review of technical documentation)
- Level of Conformity Assessment depends on classification (risk based) of the device

Devices for Special Purposes

- Member States shall not create any obstacle to devices intended for clinical investigation being made available to medical practitioners or authorized persons for that purpose if they meet the conditions laid down in Article 15 and in Annex VIII
- These devices shall not bear the CE marking.

Article 15 – Clinical Investigations

- In the case of devices intended for clinical investigations, the manufacturer or his the authorized representative, established in the Community, shall follow the procedure referred to in Annex VIII and notify the competent authorities of the Member States in which the investigations are to be conducted by means of the statement mentioned in Section 2.2 of Annex VIII.

Article VIII

- Required statement:
  - Device identification
  - Clinical investigation plan
  - Investigators brochure
  - Insurance confirmation
  - Informed consent
  - Ethics committee opinion
  - Investigation sites and staff
  - Place, date and duration of investigation
  - Statement regarding the Essential Requirements and precautions to protect patients

Essential Requirements

ER6a. Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

Annex X – Clinical Evaluation

- As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I under the normal conditions of use of the device and the evaluation of the undesirable side-effects and of the acceptability of the benefit/risk ratio referred to in Section 6 of Annex I, must be based on clinical data. The evaluation of this data, hereafter referred to as clinical evaluation, where appropriate taking account of any relevant harmonized standards, must be must follow a defined and methodologically sound procedure

Annex X – Clinical Evaluation

1. Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device where:
   - there is demonstration of equivalence of the device to the device to which the data relates and,
   - the data adequately demonstrate compliance with the relevant essential requirements;
2. Or a critical evaluation of the results of all the clinical investigations made
3. Or a critical evaluation of the combined clinical data provided in 1 & 2 above

Annex X – Clinical Evaluation

- In the case of implantable devices and devices in class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.

Annex X – Clinical Investigation

- The objectives of clinical investigation are:
  - to verify that, under normal conditions of use, the performance of the devices conform to those referred to in Section 3 of Annex I, and
  - to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device.

Annex X – Clinical Investigation

- Ethical considerations:
  - Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

Annex X – Clinical Investigation

- Methods
  - Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.

Annex X – Clinical Investigation

- Methods (continued)
  - The procedures used to perform the investigations must be appropriate to the device under examination.
  - Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device.
  - All the appropriate features, including those involving the safety and performances of the device, and its effect on patients must be examined.
  - All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

Annex X – Clinical Investigation

- The investigations must be performed under the responsibility of a medical practitioner or another authorized qualified person in an appropriate environment.
- The medical practitioner or other authorized person must have access to the technical and clinical data regarding the device.
- The written report, signed by the medical practitioner or other authorized person responsible, must contain a critical evaluation of all the data collected during the clinical investigation.

Annex X – Clinical Evaluation

- The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.
- The clinical evaluation and its documentation have to must be actively updated with data obtained from the post market surveillance.
  - Where post market clinical follow-up as part of the post market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

ISO Standards

- ISO 14155-1 Clinical investigation of medical devices for human subjects Part 1: General requirements
- ISO 14155-2 Clinical investigation of medical devices for human subjects Part 2: Clinical investigation plans

EC Guidance

- MEDDEV 2.7.1 Clinical Evaluation: A Guide For Manufacturers and Notified Bodies
- MEDDEV 2.1.1 Appendix 1 - Clinical Evaluation of Coronary Stents
- MEDDEV 2.7.2 Guide for Competent Authorities in Making an Assessment of Clinical Investigation Notification

http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/index_en.htm

Global Harmonization Task Force

- Study Group 5
  - SG5/N4:2010 – Post Market Clinical Follow-up Studies
  - SG5/N3:2010 – Clinical Investigations
  - SG5/N2R8:2007 – Clinical Evaluation
  - SG5/N1R8:2007 – Clinical Evidence

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Summary

- The manufacturer must have clinical data for the device for its intended use.
  - From existing equivalent data or a specific clinical investigation.
  - Clinical investigations must be conducted according to the Directive (Standards, Guidance)
- A clinical evaluation of the clinical data is required to support CE Marking.
- Post market clinical follow-up required unless otherwise justified.

Summary

- Notified Body is involved when the manufacturer is ready to apply for CE Marking (dependent on classification of device)
- Notified Body must assess how the manufacturer has satisfied the requirements of the Directive

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Initiated: 1964

17.C
Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

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24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

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

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

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32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

FOOTNOTE:

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

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6.10.2002

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