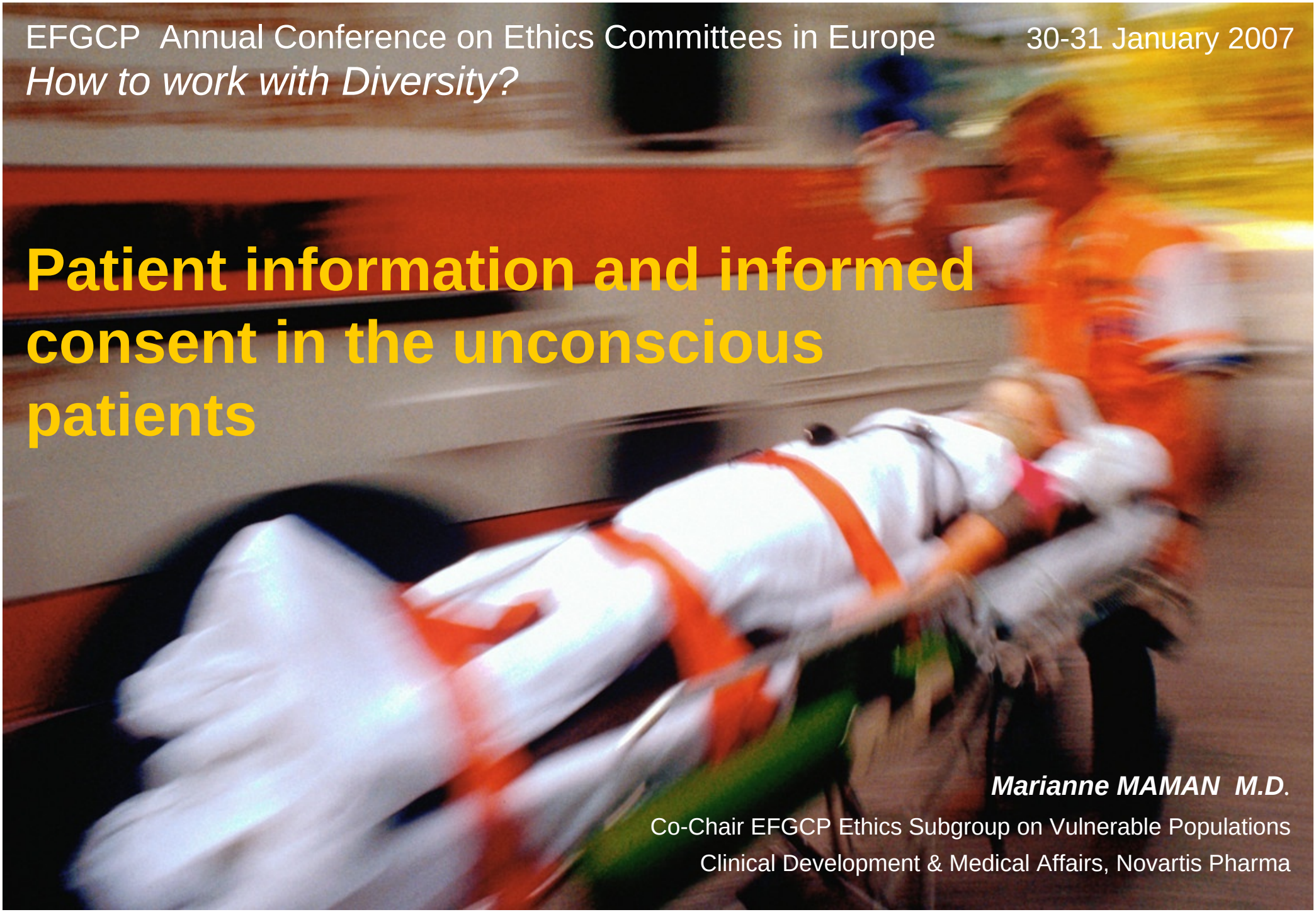
EFGCP Annual Conference on Ethics Committees in Europe 30-31 January 2007

How to work with Diversity?



Patient information and informed consent in the unconscious patients

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AGENDA

- EFGCP Ethics Subgroup on vulnerable population
- Research examples
- Research challenges (focus on consent)
- Limitations of the consent
- Alternatives to standard consent process
- Overview of major guidelines and legislations
- Summary
- Questions

EFGCP Ethics Working Subgroup on Ethical Review of Research in Vulnerable population

- To address ways in which interests of research participants are safeguarded
- Topics: research in emergency situations; elderly with impaired cognitive functions; legally incompetent; pregnancy

New members invited to join!

Issue statement

- Quality emergency research is critical to advance emergency care, further knowledge, validate data and procedures. Altogether, they contribute to saving more lives and improving (quality of) survival.
- In this exceptional situation, one of the core ethical principles of clinical research and trial participants' fundamental right have been amended.
- Conduct of emergency research poses unique challenges :
  - ✓ of dealing with a vulnerable population with no control over what happens to them and no capacity to consent
  - ✓ in a setting where the emergency circumstances leave inadequate opportunity to obtain consent from each subject's LAR
- How best address the ethical concerns raises by conducting research on non consenting individuals?
- How best address public concern?
- How best support Ethics Committees?

Research examples

- Traumatic brain injury
- Stroke
- Assisted critical care support
- Severe hemorrhage
- Complications of systemic bacterial infections
- Neuroprotection
- Advanced combat medical capabilities

Research challenges (consent)

- ***For patients***: critical, possibly life-threatening condition
- ***For medical/health care staff***: rapid decisions required in acute situations with med./surgical interventions; short therapeutic time window with need to minimize delay to treatment
- ***For family***: overwhelmed by stress if ever present and/or available
- ***For legal representative****:* may not know patient's wishes
- ***For investigators***: patient not able to give consent; work constraints and clinical research competences of emergency H/C personnel
- ***For ethics committees:*** specific competence; adequacy of consent process/form; limited guidance available
- ***For the public***: broad diversity of opinions; religious considerations

Limitations of the consent

- Consent cannot be obtained from unconscious patient
- Even if conscious, medical condition and altered cognitive functions impair capacity to understand or read long IC document
- Family and legal representative: difficulties to reach and obtain consent in emergency situations
- Question marks regarding:
  - Adequacy of information
  - Level of understanding
  - Freedom and voluntariness

Alternatives to standard consent process

- Consent from authorised representative
- Deferred consent
- Prospective consent

Consent from authorized representative (1)

- Referred to in many legislations and ethical guidelines, even if “emergency research” not always specifically mentioned
- BUT next of kin: may be too distressed to make decision
- BUT legal representative: may not know patient’s wishes
- Need to acknowledge constraints and limitations
- Need to act in individual patient’s best interests

Deferred Consent

- Mentioned in several guidelines e.g. Declaration of Helsinki
- Acknowledge that standard consent not possible and that research is critical to advance knowledge and benefit patients
- Obtain consent later from patient to continue participation when (s)he recovers, or from legal representative
- BUT too late for decisions made earlier w/o his/her knowledge and agreement
- What kind of disclosure if patient dies? What about litigation?

Prospective Consent

- Identify and inform potential research participants
- Where possible, obtain advance consent
- BUT
  - ❖ may require substantial numbers of consent
  - ❖ likelihood of event (e.g. trauma) may be underestimated
  - ❖ How to target population concerned
  - ❖ How to ensure quality of information delivered and understood
  - ❖ How to identify those consented

What do major guidelines say regarding patients from whom informed consent cannot be obtained ?

Declaration of Helsinki (para.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 the informed consent is a necessary characteristic of the research population
- The specific reasons for involving research subjects with condition that renders them unable to give consent should be stated in the protocol for consideration and approval of the EC.
- The *protocol* should state that *consent to remain* in the research should be *obtained ASAP from* the individual or legal representative

What do major guidelines say regarding patients from whom informed consent cannot be obtained (2)?

CIOMS Guidelines

- When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risks from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons.
- Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increase and when an ethics committee has approved them.

What do major guidelines say regarding patients from whom informed consent cannot be obtained (3)?

ICH-GCP for patients in emergency situations (4.8.15)

- The consent of the subject's legally acceptable representative (LAR) , if present, should be requested.
- When the subject's LAR is not available, enrolment of the subject should require measures described in the protocol or elsewhere , with documented approval/favorable opinion by the IRB/IEC to protect the rights, safety and wellbeing of the subject and to ensure compliance with applicable legal requirements.
- As soon as possible, the subject or the subject's LAR should be informed about the trial and consent to continue.

What do major legislation (EU) say regarding patients unable to give consent (4)?

EU Clinical Trial Directive 2001/20/EC (ER not mentioned explicitly)

- Special protection afforded. “incumbent on the MS to lay down rules to this effect”
- Only if such research cannot be performed in subjects who can consent
- Only if research relates to life-threatening or debilitating clinical condition from which the patient suffers
- Only when expected direct benefits to patients outweigh the risks
- Consent from the legal representative defined broadly as natural or legal persons, an authority and/or a body provided by national law
- Consent given by legal representative to represent patient’s presumed will
- No incentives or financial inducements
- Study design to minimize pain, discomfort, foreseeable risk (risk threshold/distress)
- Endorsement from EC with expertise in the field

What do major legislation (EU) say regarding patients unable to give consent (5)?

Convention on Human Rights and Biomedicine (add. Protocol art.19)

1. The law shall determine whether, and under which protective additional conditions, research in emergency situations may take place when a person is not in a state to give consent and because of the urgency of the situation , it is impossible to obtain in a sufficiently timely manner, authorization from his/her representative or an authority or person or body which would be called upon to give authorization
2. The law shall include the following specific conditions:
   i) research of comparable effectiveness cannot be carried out on persons in non-emergency situations; ii) the research project may only be undertaken if it has been approved specifically for emergency situations by the competent body; iii) any relevant *previously expressed objections of the person known to the researcher* shall be *respected;* iv) *acceptance of group benefit if there is minimal risk and burden* for the patient
3. Persons participating in the ER project or if applicable their representatives shall be provided with all relevant information concerning their participation as soon as possible. *Consent or authorization for continued participation shall be requested as soon as reasonably possible.*

What do major legislation (USA) say regarding patients unable to give consent (6)?

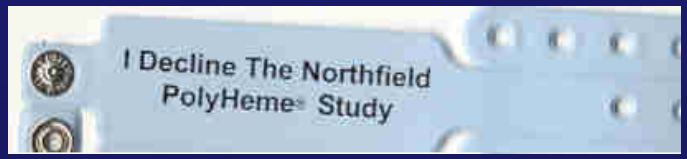
- FDA Draft Guidance “For IRB, Investigators and Sponsors: exception from IC requirements for emergency research” July 2006
- FDA Public Hearing held Mid-Oct. 2006 on emergency research conducted w/o IC under FDA’s emergency research rule
- Goal: determine adequacy of existing framework –whether modification required
- Emergency Research protocol submitted for review under US regulation (21CFR50.24)
  - ✓ undergo added IRB oversight and require
  - ✓ Community consultation
  - ✓ Public disclosure
  - ✓ Independent Data Monitoring Committee
- New draft (initial posted in 2000): more specific roles of IRB, investigators, sponsors and more details about appropriate community outreach

Focus on part of US ethical framework

- Community consultation
  - ✓ Inform that consent not obtained for most (or all) subjects
  - ✓ All relevant aspects inc. risks and benefits
  - ✓ Perspectives of communities on proposed research
  - ✓ Ways in which those whishing to be excluded can do so

It requires active collaboration between sponsors, investigators and IRB

- Public disclosure
  - ✓ Dissemination of information about proposed research to communities
  - ✓ Also includes post study information



Summary

- If patient to trust physician to use unproven intervention as innovative therapy, such trust can extend to using same intervention as part of well-designed, controlled and monitored study after review/approval by ECs
- The Consent: a process, not an end in itself
- Safeguards in place to protect:
  i) patients from harm; ii) right to be treated in an optimal way
- In emergency settings:
  - ✓ patients cannot be active participants in choosing interventions
  - ✓ Physicians must act on patients' best interests (and their wishes if known)
- Harmonization of guidance desirable regarding consent form and process across EU and between EU and USA

Summary(2)

- Clarification desirable regarding the role and definition of the legal representatives
- Pro-active (e.g. community consultation, public disclosure) and on-going activities during research (including deferred consent) may contribute to strengthening safeguards and to increasing trust if adequately handled
- Patients' best interests to prevail over other considerations
- Importance of expertise in emergency medicine at all levels including ECs
- Pro-active collaboration between sponsor, investigators, H/C staff, ethics committee and regulators required
- Information and education of the public beyond any given trial critical to ensure future and success of emergency research

Questions for the Workshop

- Participation breakdown:
  - ✓ Ethics committees, investigators, regulators industry, others
  - ✓ Experiences in emergency research
- What are the best Informed Consent Form and process?
- What would be the key requirements to ensure adequate community consultation and public disclosure? How would you optimize them?
- Are there other safeguards that would ensure patients' protection (e.g. local best practices)?
- What are the means which would best support your activities as EC's member when reviewing an emergency research?
- What are the key priorities/topics for an ethical guideline at the EU level?