

THE EUROPEAN DIRECTIVE FOR CLINICAL RESEARCH

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

- **the European intensive care community is deeply worried**

because...

- **the Directive will stop practically all randomized, controlled clinical trials in intensive care in Europe**
- **the Directive will make future interventional, and especially, randomized, controlled clinical trials in intensive care impossible in Europe**
- **the Directive makes research in emergency situations impossible in Europe**

WHERE ARE THE PROBLEMS ?

- intensive care patients are practically never capable of giving an informed consent
- requirement for a legal representative
- implicate requirement for anticipated benefit for the individual trial subject

2. A clinical trial may be undertaken only if, in particular:

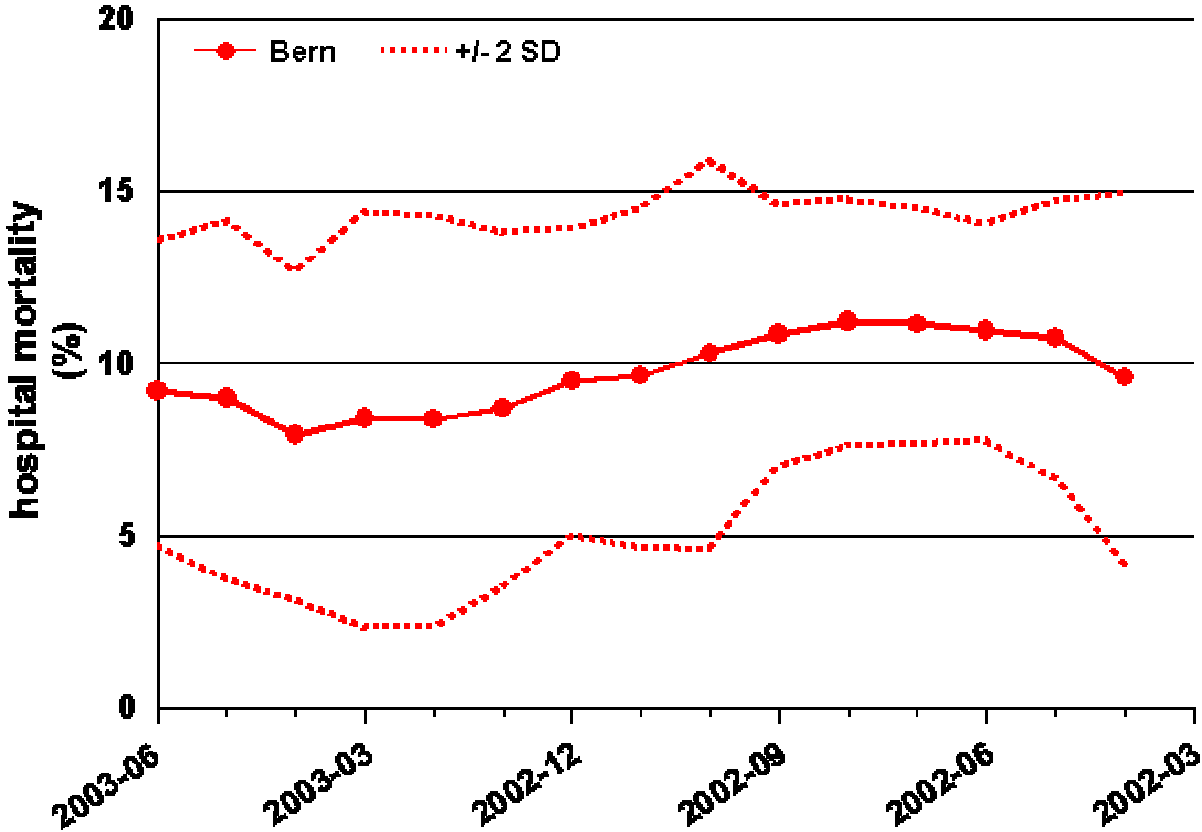
(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical

WHERE ARE THE PROBLEMS ?

- **intensive care patients are practically never capable of giving an informed consent**
- **procedures for defining a legal representative in research situations do not exist in most European countries**
- **much of interventional clinical research in intensive care has the character of emergency research**
- **obtaining an informed consent for a legal representative in emergency situations is impossible**

INTENSIVE CARE PATIENTS HAVE A HIGH RISK OF DEATH

APPROXIMATELY 300 DEATHS / YEAR,
equals ~ 60 % of annual road traffic deaths in Finland



NECESSITY OF EMERGENCY RESEARCH: an example from a multicenter trial

- **development of treatment protocols for multicenter use in intensive care**
- **survey of events triggering therapeutic interventions**

⊗ **five ICUs in Europe**

⊗ **four ICUs in the US**

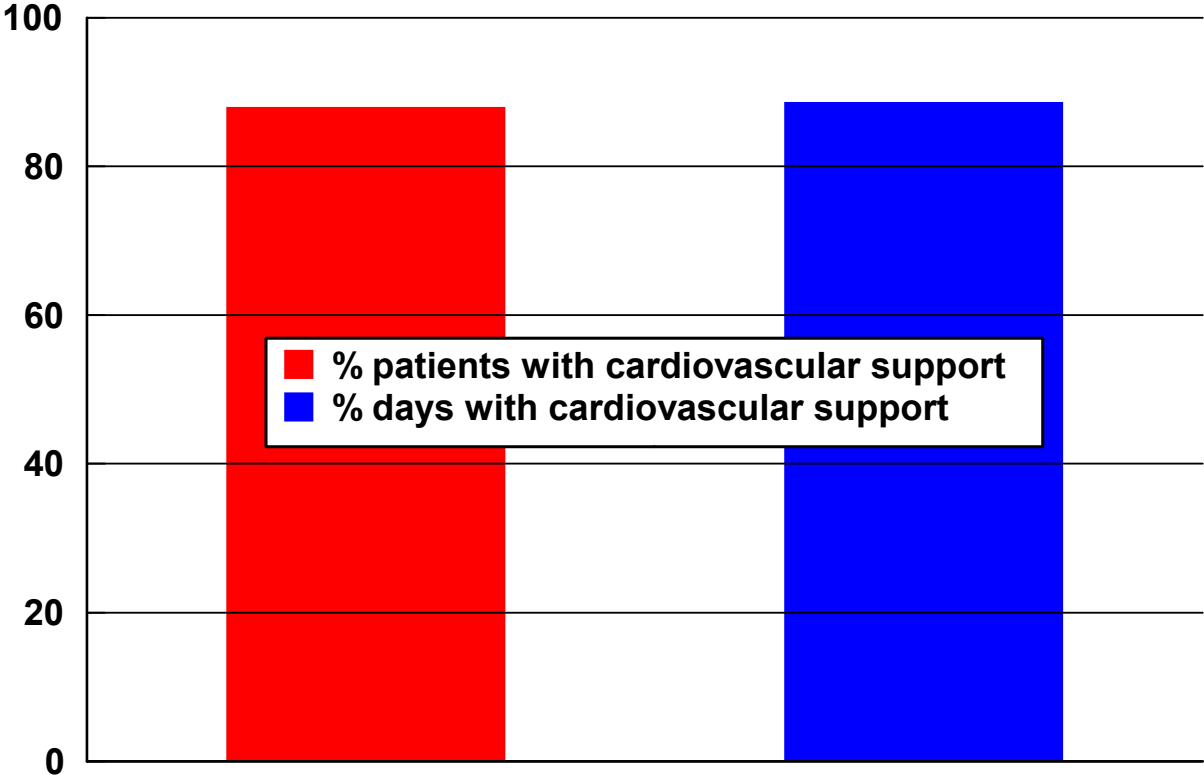
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NECESSITY OF EMERGENCY RESEARCH



451 patients with sepsis or after cardiac surgery

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A European Directive for clinical research

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Introduction

After a long process the European Parliament and Council adopted on 4 April 2001 a directive on "the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" [1]. Even if phy-

Clinical trials on medicinal products

The directive is applicable only to the conduct of trials involving drugs and other medicinal products (Article 1.1). The basic architecture of the text is derived (Article 1.2) from the set of recommendations known as "Good Clinical Practice" (GCP), published and regularly updated by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (<http://www.ich.org/pdf/ICH/e6.pdf>). There is currently in Europe a great variety of situations concerning the legislation for clinical research: Belgium has no law at all, Spain has a regulation only for drugs, while The Netherlands, France, and Germany have laws which concern all types of research involving human beings. Each of the Member States will have to delineate the extension of its legislation concerning clinical research. For instance, France has already made the choice that the implementation of the directive would apply to all types of clinical research.

large randomized controlled trials, but this provision will become mandatory for all types of trials.

Authorization

A trial cannot start until the ethics committee has issued a favorable opinion (Article 9.1), which is certainly not new. However, Article 9 also states that authorization is required from a "competent authority," usually a special administrative body different from the IRB, such as in France, the National Drug Agency. This obligation already exists in several European countries but not in all, for example, in The Netherlands. It is specified in the directive that the authorization does not need to be specifically formulated, and that a trial may start after 2 months during which "the competent authority" has not informed the sponsor of any grounds for nonacceptance." To save time, the submission to the ethics committee and to the authority may run in parallel.

A PRACTICAL EXAMPLE: the case of severe sepsis

ESICM (European Society of Intensive Care Medicine), ISF (International Sepsis Forum) and SCCM (Society of Critical Care Medicine) launched the “Surviving Sepsis”-campaign in 2002, with goals to

- **Increase awareness, understanding and knowledge**
- **Change perceptions and behaviour**
- **Increase the pace of change in patterns of care**
- **Influence public policy**
- **Define standards of care in severe sepsis**
- **Reduce the mortality associated with sepsis by 25% over the next 5 years**

A PRACTICAL EXAMPLE: the case of severe sepsis

SEVERE SEPSIS

- **Sepsis is caused by the body's reaction to infection**
- **Severe sepsis is a complex and often life-threatening condition**
- **It can affect anyone, but often develops in patients with pneumonia, trauma, surgery, burns or cancer**
- **Septic shock is an acute circulatory failure caused by sepsis**

<http://www.survivingsepsis.org/>

A PRACTICAL EXAMPLE: the case of severe sepsis

QUICK FACTS

- Over **18 million** cases of severe sepsis worldwide each year²
- Up to **135,000 European** and 215,000 American deaths each year^{2,7}
- Sepsis kills approximately 1,400 people worldwide every day⁵
- Severe sepsis is the leading cause of death in the non-coronary ICU⁵
- **Each year sepsis costs €7.6 billion in Europe** and €17.4 billion in the US^{2,5}

<http://www.survivingsepsis.org/>

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*WILL STOP ALL INTERVENTIONAL CLINICAL RESEARCH
IN SEPTIC SHOCK*