

**Ethical issues, the Impact of the
Clinical Trials Directive and Good Clinical
Practice, and publication ethics in the ethics
review process in Europe in 2011**

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Background

- Ethics is a concern for us everyday: Energy use, fuel use, organic food, travel.
- However, the most common ethical challenges in the European Commission are in proposals related to health programs or directorates involving **research with people** (e.g. programmes such as Food, Security, ERC Marie Curie)
- A major change in FP7, compared to FP6, is that the ethics review is critical element, and its also always an evolving field with new ethical issues in new research grant proposals as science advances.

Why bother with research ethics?

- **Tuskegee Syphilis Study**

From 1932 to 1970, 400 low-income mainly illiterate African-American males recruited into longitudinal study of syphilis. Participants given free medical exams and meals, and burial insurance **(but only if they agreed to an autopsy)**. Physicians told patients being treated for “bad blood”

Penicillin was found in 1947 effective for syphilis, **however, the study participants were not treated with antibiotic and withheld treatment for over 25 years**

No informed consent obtained, placebo treatment given but no consent to this, spinal taps given but patients were told **this was treatment** not diagnostic testing



Some of the Tuskegee Study Group clinicians note: not all involved.

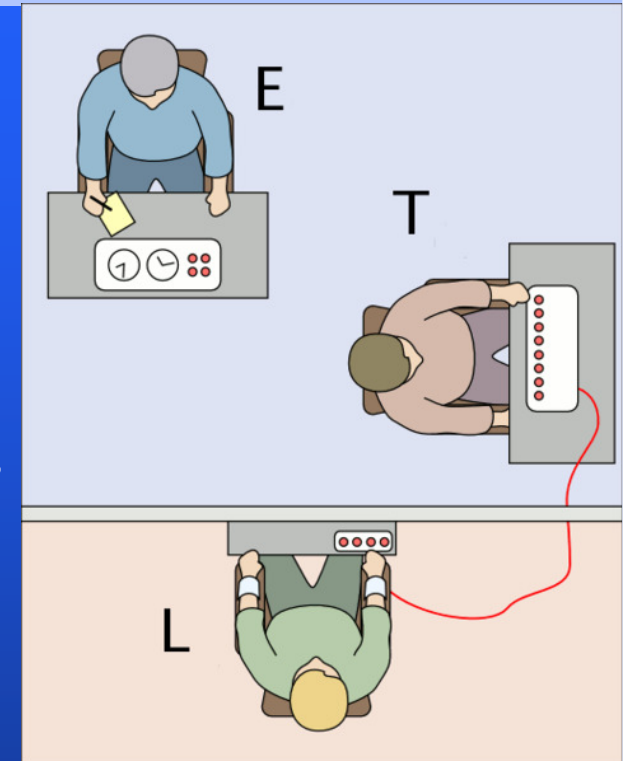


**So can all medical
Doctors be trusted?**

Why bother with research ethics (cont)?

Stanley Milgram's (Social Psychologist) famous conformity experiment (1963)

- Participants were asked to give increasingly severe electric shocks (scale: 15-450 volts) to someone supposedly trying to learn a series of word pairs.
- In fact, the 'learner' was an actor and no shocks were given, but they screamed as if they were in increasing amounts of pain, while the experimenter ordered the participant to increase the voltage.
- The experiment tested how far someone would go in giving pain to another human being when being ordered by an authority figure. 65% of participants continued despite indications that the 'learner' might be unconscious or dead.
- Major stress for the 'participants', now classed as unethical study



So can all

Psychologists

be trusted?

Why very occasionally do researchers act in such unethical ways or make ethical mistakes?

- These examples **are very rare cases** most research is ethically acceptable!
- In other cases, researchers may be initially:
 - Unsure of certain ethical rules and legal framework
 - Most make genuine mistakes
 - Mentally or physically unwell
 - Busy people with limited time for focus on ethics and trust other collaborators
 - Lack of good training in ethics or research
 - Pressures to **"publish or perish"**. Sometimes publishing results can lead to promotion, extra salary, larger grants, larger department, better chances to collaborate and travel, etc

When is Ethics Approval Required?

- My focus:

**When you use a human in
any way in a research
manner**

Special populations (extra attention to ethics here)

- **My focus today = Clinical Trials (the most expensive, but valuable of research studies)**

- Research involving children



- Research involving vulnerable adults

- Research Involving Pregnant Women

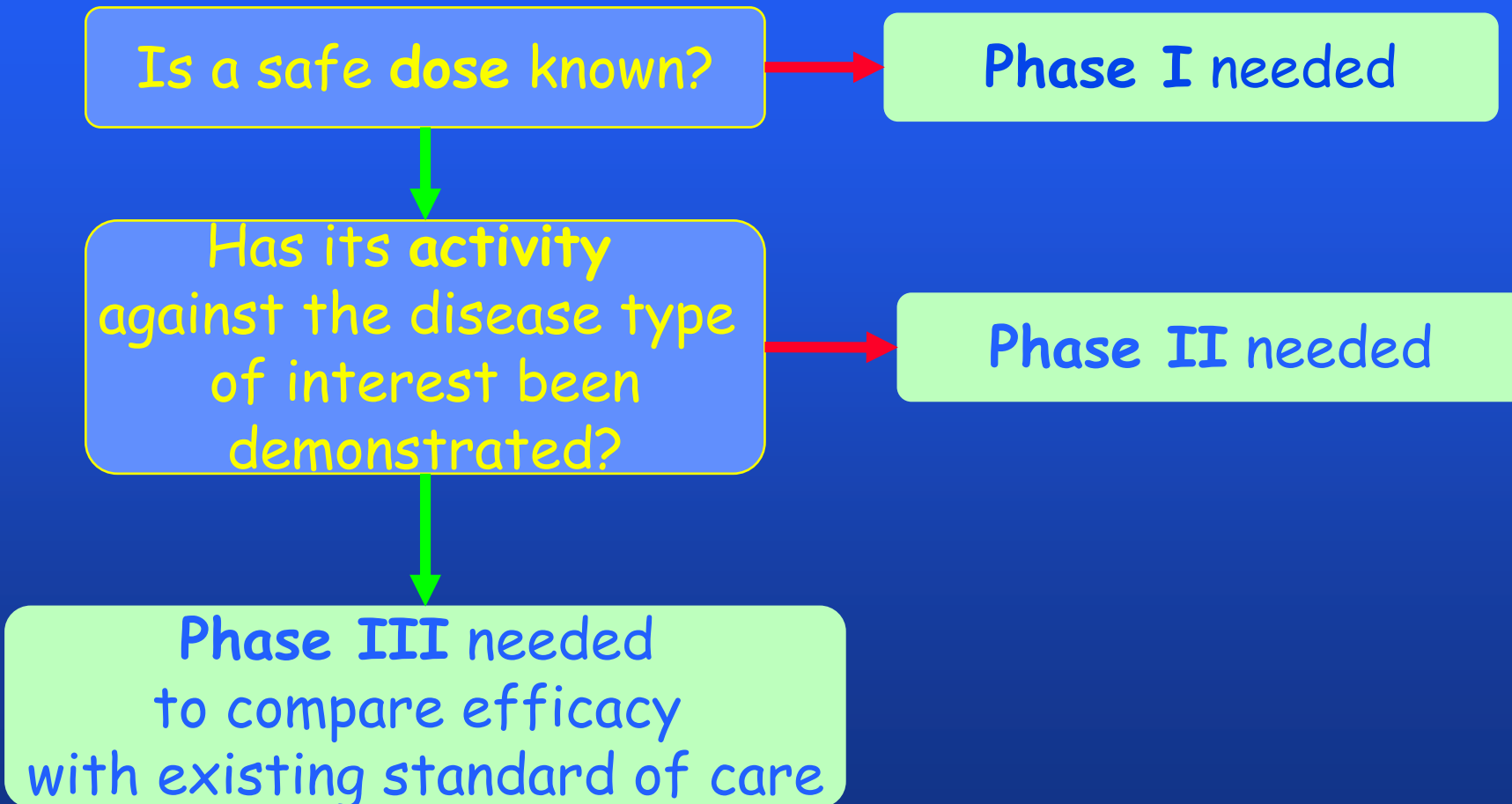


- Research Involving Interventions with Participants from Developing Countries

Clinical Trials

- A clinical trial is a research study [conducted in patients] to answer specific questions about new therapies or new ways of using known treatments. Typically done in drug treatment studies
- Clinical trials are used to determine whether new drugs or treatments (therapy, intervention, etc) are both **safe and effective**.
- Carefully conducted clinical trials are the fastest and safest way to find treatments that work.

Phases of Development of Drug studies



Patient informed consent and patient information form for clinical trials

Elements for Participant Information Sheet in Clinical Trials

- **Study title**
- **Investigators' names and contact details**
- **Introduction**
- **Purpose of study**
- **Study procedures including what participants will be asked to do/time commitment**
- **Eligibility to participate**
- **Risks and any debriefing arrangements as required**
- **Clause regarding voluntary participation**
- **Clause regarding stopping the study if events indicate**
- **Treatment and compensation for injury**
- **Possible benefits of participation**
- **Details of data collection, storage, use and disposal**
- **Informing participants of access to research findings**
- **Provide the details of the ethics approval**

What should be on the informed consent form? A more detailed overview

- Patients' right to withdraw at any time without any consequences.
- It must be **understandable to the lay person** (not degree educated level).
- Voluntary participation (crucial). How does a patient with severe brain injury give consent to new possible beneficial research?
- No threat or excessive inducements (see past examples)
- No improper reward – e.g. It is responsible to pay costs or local fees but not more, it can be seen as an inducement (for those in need)

So what does the European Clinical Trials Directive (2001/20/EC) add for researchers?

- Full title is: Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for **human use**
- Needed to harmonise standards for clinical trials (good intention)

Key aims of the Clinical Trial Directive

- To protect patients, by providing a legal basis for many aspects of clinical research
- To harmonize clinical research procedures across Europe
- Overall impact:
 - creates more “level playing field” across the EU
 - most substantial change in conduct of clinical trials in Europe since ICH
 - but variations will still exist between Member States in many areas of clinical research

Key Changes for Researchers

Applies to all clinical trials (Phase I-IV) involving intervention

Investigational Medicinal Products (IMP) manufactured according to Good Manufacturing Practices (GMP)

Administration of Regulatory and Ethics processes significantly changed (slow and variable)

Other changes:

Established a Central EU database (Eudract)

Safety reporting requirements

Consent process (certain vulnerable groups)

But the Challenges remain years later

- Years of debate about increased cost and time
- Debate about increased safety and added protection for patients
- Increased cost and impact on academic research organizations has been huge
- Debate if it created environment not ideal for academic clinical trials
- Better harmonization of regulations and ethics across member states may not have been as hoped
- Better safety monitoring across member states and protection for patients
- Same standards for academic and industry trials are difficult to impliment with same level of funding

Lead article in Breast International Group Journal, December 2009

FEATURE THEME

EXPERTS SAY WAY FORWARD FOR CLINICAL TRIALS REGULATION IS NOW CLEAR

BY EMMA ROSS

Key opinion leaders agree that it is now time to get on with revising and simplifying regulations to ensure the healthy future of clinical research in Europe.

There has been much angst and protest from the academic research community over the European Union's clinical trials directive since its adoption in 2001. Leading clinical investigators predicted early on a threat of decimation of independent research in Europe and, soon after its implementation in 2004, began highlighting how the legislation is hindering non-commercial research and resulting in the opposite of what it set out to do. A steady stream of evaluations, journal correspondence and editorials continues to illustrate how the directive has increased bureaucracy and costs, slashed the number of academic trials conducted, driven away budding-career trialists and slowed the delivery of cutting-edge care to patients.

It is Time to Act

But five years on from its implementation, key opinion leaders agree that there is no need for any further analysis of the directive's problems and that it is now time to get on with revising and simplifying regulations to ensure the healthy future of clinical research in Europe - particularly by amending them to take into account the fact that not all clinical trials pose the same risk.

"The impact of the directive is now clear. There's no more need to do these sorts of 'what's the problem' reviews," said Professor Richard Sullivan of the King's Health Partners Integrated Cancer Centre in London. "The two definitive reports on the policy recommendations have now been completed in the last few months, and with these, we really have the way forward. People have got to act on this now and stop saying let's have another review."

"One of the reasons that Europe is very competitive is that it has a very strong public sector and it's very creative."

"WHAT WE ARE GOING TO SEE IF WE DON'T DO WHAT'S NEEDED IS A MASSIVE REDUCTION IN CREATIVITY AND A VERY UNIDIMENSIONAL EUROPE WHICH SIMPLY CHURNS THROUGH A CERTAIN NUMBER OF COMMERCIALLY DRIVEN TRIALS A YEAR"

said Sullivan, who is also chairman of the European Cancer Research Managers Forum, which studies cancer research and funding in Europe.

The European clinical trials directive aimed to cut red tape, improve patient protection and enhance the quality of drugs and clinical research. By 2006, all 27 EU member states had implemented it into national legislation. However, many experts say the directive has failed in its objective, providing no improvement to patient safety and hindering research by piling on administrative burden, which has driven up costs, especially for multi-country studies.

"One can point to things that have been improved as a consequence of it, but the net effect has been very substantially destructive," said Professor Rory Collins, co-director of the Clinical Trial Service Unit at the University of Oxford in the UK.

Sullivan said estimates of the impact of the directive on costs have become more solid over the last few years and that costs seem to be about 2.6 times higher than they used to be. While some may argue that some of the trends in costs increase were happening anyway, the curve became so steep after the directive that there has undeniably been a real effect, Sullivan said.

The extra administrative and cost burdens have resulted in fewer trials being conducted in Europe, experts agree. Sullivan says it looks

as if there's been a one-third reduction overall, but that few countries have good baseline data.

"There's no doubt that some of those should have been lost, but we will never know the lost opportunity - how many trials have not happened that should have," he said.

The effect on trial activity levels seems to have been variable across countries and research groups. Dr Brian Moulton, chief executive of the All-Ireland Cooperative Oncology Research Group (a member of BIG), says that in Ireland academic trial activity has dropped by over half since the directive took effect. Others have managed to adapt over the last five years.

The European Organisation for Research and Treatment of Cancer (EORTC), which runs about 50 clinical trials a year, says it initially experienced a significant dip, but that levels have recently recovered.

"In 2005 - 2006, after the directive, our number of new clinical trials dropped by 50%, but since then we have learned how to address the issues and we are more or less back to the volume of clinical trials that we had, but the cost has increased



What is the added ethical value from the CT Directive?

**Persons who are incapable of giving legal consent
to clinical trials should be given special protection**

Articles are present in the Directive to cover:

Protection of clinical trial subjects

Clinical trials on minors

**Clinical trials on incapacitated adults not able to
give informed consent**

So how do we help applicants deal with ethics?

- **Remember typically researchers often undergo limited formal ethics training in university**
- **Ethics rules are always evolving as science evolves**
- **Be aware ethics can be a combination of science and art and thus everyone may have different interpretations and views. Small degrees of differences of opinion can often cause heated ethical debates.**

How can you help an applicant have a complete and good FP 7 ethics proposal?

- Advise the applicant that all relevant FP7 ethics questions have to be answered and pages numbered and be complete: poor ethics applications **may** well weaken at the scientific evaluation panel review
- **Refer applicants to key web sites such as** HEALTH-NCP-NET www.healthncpnet.eu with example Informed Consent form, details of procedures, common practices, data protection, GCP, etc
- Ask applicants not to **cut and paste** from old applications, scientific and ethical reviewers see this and have unfavorable opinions on this approach

After an FP 7 project is finished has ethics ended? – No! *

- **Years of clinical research has lead to the new field of “publication bias” (Topic in FP7 with new projects selected)**
- **Publication bias can have major ethical impact on researchers and society**
 - **None publication of positive results (e.g. ASCO- 25%)**
 - **None publication of negative results (Difficult for authors)**
 - **Repeat publication of results (salami slicing)**
 - **Repeat presentation of same results (perhaps in different languages or parts of the studies)**
 - **Selective presentation of results (only certain endpoints)**

*** Disclosure - I am an editor of 2 research journals and on the editor board of 8 journals including advisor for The Lancet and Lancet Oncology**

Is publication ethics really a problem?

- Read Richard Smith's book (25 years editor of BMJ) 'The trouble with medical publications' which raises many ethical challenges for us all:
- Concerns about peer review
- Concerns about funding (who, when, where and why)
- Concerns about ghost authorship
- Concerns about duplication publication
- Concerns about lack of open access

Is this simply a UK problem? See Dr. DeAngelis, *JAMA*'s editor

- **After over 10 years as Editor of JAMA has concerns that:**
- **Negative results don't get published**
- **Positive results get published**
- **Concern about independence of results**
- **Concerns of possible industry influence on research**
- **Result: An increasing number of editors and authors now need to read articles in peer reviewed journals with great care**

What are we doing about this

- **Journal editors now ask authors for the health research protocols for studies which must be registered if a trial of not published (avoids repeated analysis or analysis of different endpoints)**
- **Journals has policies for COI for editors, reviewers and authors that help ensure the integrity of the peer review process**
- **WAMA, ICJE all have guidelines on ethics of publications ethics that must be followed**
- **How can this impact on you: keep track of the field of publication ethics by reading new articles on publishing results**

Summary

- **Ethics committees are here to stay and play a key role of oversight and the protection of patients; Variability in their recommendations are a norm**
- **The Clinical Trial Directive is here to stay and while adding cost and administration, should help standardize and protect patients.**
- **Getting ethics correct in a research proposal needs time to be built in the grant writing cycle and applicants need to plan for this**
- **Ethics experts can help, but most ethical issues SHOULD already be understood by the investigator**
- **Poor ethics can make a good scientific proposal look poor quality**
- **Ethics does not stop at the end of the study: Make sure good publication practices are followed**

Questions

**Thank you and
questions...?**