Compassionate use and ethics committees

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ETHICS COMMITTEES

- Review by independent ethics committees (ECs, also called institutional review boards – IRBs) is a generally accepted ethical and legal principle for **biomedical research**

- This principle is contained in all major international ethical guidelines including the Declaration of Helsinki, the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research, the Guideline for Good Clinical Practise by the International Conference on Harmonisation, and the International Guidelines for Health-Related Research Involving Humans (CIOMS)

ETHICS COMMITTEES

- The overall objective of ECs is „*to safeguard the rights, safety, and well-being of all trial subjects*” (the Additional Protocol)
- To that end ECs:
  - review protocols
  - evaluate documents and procedures related to the informed consent process
  - review subject recruitment procedures
  - verify the qualifications of the principal investigator
- While the role of ECs in the review of biomedical research is commonly accepted, this is not the case with **compassionate use** (CU)

ETHICS COMMITTEES AND CU

- In most countries independent ethical review of CU is not required
- EC approval is mandatory in very few countries including **the US, Italy,** and **Poland**
  - the US – CFR Title 21 part 312 subpart I
  - Italy – Decree of the Ministry of Health (2003)
  - Poland – the Act on the Professions of Doctor and Dentist (1996)
- In **Australia** – review is required, but only in case of **programs involving groups of patients**; for treatment of individual patients this is not necessary

EMERGENCY CU - FDA

- In the case of **emergency CU**, it is not necessary to wait for IRB approval to begin treatment. However, the IRB must be notified of the emergency CU **within 5 working days** of emergency use.
- Any **subsequent use** of the same drug **at this institution** is subject to IRB review *(CFR, section 56.104(c))*

EMERGENCY CU - FDA

Table 1. Distribution of Expanded Access IND Types Submitted to CDER From 2005 Through 2014.

Type of IND	Number
Single-patient IND, nonemergency (SPIND)	5284
Single-patient IND, emergency (eIND)	5511
Intermediate-size IND	116
Large population treatment IND	28
Total	10 939

Jarow et al., 2016

DECLARATION OF HELSINKI AND CU

- In the **treatment** of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with **informed consent** from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should **subsequently** be made the object of **research**, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available

Article 37 (Unproven interventions in clinical practice)

NATIONAL CODES OF MEDICAL ETHICS AND CU

- Of national codes of medical ethics of English-speaking countries (the US, Canada, the UK, Ireland, Australia and New Zealand) only three (of **the US, Australia** and **New Zealand**) contain articles that can be interpreted as referring to CU

- Only one of these (of **New Zealand**) states that use of new (and apparently unproven) drugs can have **research aspects**; thus „*in each case the physician should consider whether it should be subject to formal procedures typical of clinical research*”

WHAT DO WE KNOW ABOUT THE WAY ECs DEAL WITH CU APPLICATIONS

- So far, only one study has been performed to evaluate how ECs deal with CU applications *(Montanaro et al., Eur J Clin Pharmacol, 2017)*
- In the period 2010-2015 the EC of the University Hospital of **Bologna** received **610 CU applications**
- While clinical trial proposals are reviewed by this committee during plenary meetings once a month, decisions regarding authorization of CU requests are made by a **working group** of the committee usually **within 72 h**; favorable opinions of the group are immediately available for execution.

- The application must contain the following elements:

1) **Clinical description** of the patient illness and his/her status, including lack of response or intolerance to previous treatment(s) or their unavailability
2) **Declaration of free supply** signed by the producer of the requested medicine;
3) **Investigator brochure** of the medicine
4) **Guidance** for the compassionate use of the medicine
5) **Information sheet** for the patient
6) **Informed consent** form
7) **The letter for the GP**, when applicable
8) **CV** of the applying Doctor

- Two very important tasks of the working group include:

    1. to ascertain the **lack of valid alternative drugs**
    2. to verify whether **phase III** (or in some cases **phase II**) **clinical trials** have been completed or are ongoing

- Out of 610 applications **only 6 were rejected**, usually because they did not meet the requirements of the national regulations on CU

- **Arguments against ethical review of CU:**

  - CU is primarily a kind of **treatment** and not biomedical research

  - possible **delay**

- **Arguments for ethical review of CU**:

  - CU often involves significant **research aspects**

  - CU involves use of drugs with **unproven safety and efficacy**

  - informed consent

  - qualifications of a physician

  - fair patients selection

CU AS TREATMENT

- According to both the FDA and the EMA, CU is primarily a kind of **treatment** rather than biomedical research
- „*The primary purpose is to diagnose, monitor, or treat a patient's disease or condition*" (CFR Title 21 part 312 subpart I)
- „*Although safety data may be collected during compassionate use programmes, such programmes cannot replace clinical trials for investigational purposes. Compassionate use is not a substitute for properly conducted trials*"

(the Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use (CHMP) of the EMA)

RESEARCH ASPECTS OF CU

- In practice CU often involves significant **research aspects**
- At present these are found particularly in **programs involving groups of patients**
- In recent years such programs, including those that involve large groups have increasingly been carried out to obtain data on efficacy and safety of investigational drugs in **„real-world" settings**
- Research aspects of these programs are a very important argument for a necessity for EC review

DRUGS USED IN CU

- In principle CU may involve use of an investigational drug at **any stage** of its clinical development
- This raises a question of **safety and efficacy** of investigational drugs
- For investigational drugs, the phase transition probability was estimated at:

  59.52% (Phase I-II)
  35.52% (Phase II-III)
  61.95% (Phase III-New Drug Application (NDA) Submission)
  90.35% (NDA Submission-NDA Approval)

DiMasi et al., 2016

DRUGS USED IN CU

- **Safety concerns** (including toxicity) accounted for 20.5%, while **lack of efficacy** accounted for 35.3% of failures (DiMasi et al., 2001)
- Some authors suggest that the percentage of investigational drugs that were abandoned at different stages of clinical trials due to safety concerns may be even higher (Jacobson and Parmet, 2007)
- Out of 640 investigational drugs in late-stage clinical development, **54%** failed during or after pivotal clinical trials; most of these failed due to **inadequate efficacy** (57%) or **safety concerns** (17%) *(Hwang et al., 2016)*

DRUGS USED IN CU

- Any use of investigational drugs (even those from late-stage clinical trials or undergoing review by a regulatory agency) may be associated with **significant safety and/or efficacy concerns**

- An important role of an EC should be to evaluate **whether potential benefits justify exposure of a patient to risks** associated with use of a drug with unproven safety and efficacy

FAIR PATIENTS SELECTION

- Compassionate treatment involves use of investigational drugs and thus is **not a part of standard clinical care**
- Consequently, a problem of **inequity** in access of patients to CU programs may arise
- Therefore, **fair patients selection** is considered one of the most important ethical challenges of CU *(Caplan et al., 2016)*
- **Ensuring that selection of patients is fair** should be another important task for ECs
- Access to unapproved drugs should be dependent on **medical criteria** only

CONCLUSIONS

- Currently EC approval of CU is required by law in very few countries
- Detailed ethical guidelines on CU are generally lacking
- There are arguments both for and against an involvement of ECs in review of CU applications, but the former seem to outweigh the latter