Access to investigational drugs outside of controlled clinical research – individual and social interests

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Goals

There is a growing public and regulatory support for compassionate use / extended access programs.

In this talk I will try to examine what constitute a valid ethical justification for such access to unproved drugs

- principle of beneficence
- principle of respect for autonomy
- principle of justice

Justification [1]

Beneficence	**Duty to rescue** [Edwards 2013]
	Physician's professional duty to care [Edwards 2013; Ruderman et al. 2006]
	Compassion [Walker et al. 2014]

Compassion

- **What is compassion?**
  - emotion (*caritas*)
  - disposition, virtue
  - proactive attitude towards the suffering of others
  - manifestation of care as a „moral afford” to respond to the needs of others
  - moral duty
- **What is its normative force and scope?**
- Maybe it is just a „label” for the mixture of different psychological phenomena, such as empathy & egoistic fear; sense of obligation towards others & wish to push a danger away…

Duty to rescue

General duty to rescue	Institutional duty to rescue	Professional duty to rescue
Applies to all moral agents as such.	Applies to institutions (governments) responsible members of the collective.	Applies to representatives of a given profession and is more stringent.
„If someone can prevent a serious harm to another person at minimal cost to herself, then she has a moral duty to do so".	„If an institution can prevent a harm to group of people, it is responsible for, without violating demands of fairness towards other institutional members, then the institution has a moral duty to do so".	„Given the professional role of physician, as defined by tradition, professional ethos and regulatory requirements, **if a physician can prevent a serious harm to a patient, without exposing herself to risk of serious harm, then she has a moral duty to do so**".
What is the force, scope and justification of this duty?	**Does international community have a institutional duty to rescue victims of local public health emergencies?**	**How does it apply to situations in which there are no proven, safe, and effective measures to prevent the patient from harm?**

[Sheehan 2007; Rulli & Millum 2013]

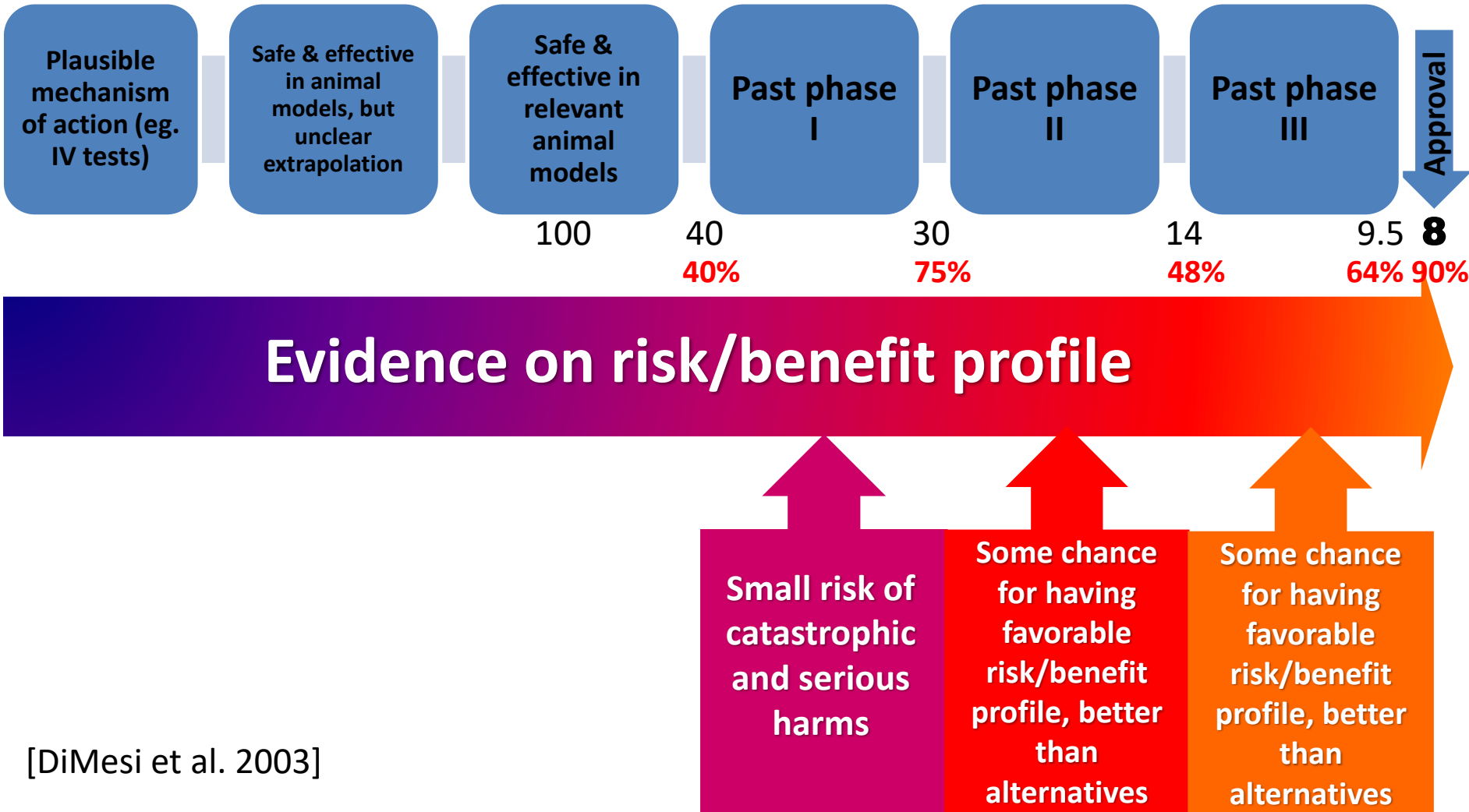
Professional duty to rescue/care

- The duty seems to actualize only when a physician **can help**, namely when there are solid scientific evidence that a given intervention would benefit the patient.
- **Undoubtedly, the duty applies to standard care in which registered medicinal products (devices or procedures) are used.**

Clinical use of unproven interventions

- Clinical use of unproven interventions constitutes a **significant deviation from the standard care.**
- **Rule:** **„A doctor can provide a patient with a nonstandard care only when doing so is reasonable and is in the best interests of the patient”.**
  [Menikoff 2006: 42. See also: WMA Declaration on Professional Autonomy…; Declaration of Helsinki: 37: „..it offers hope of saving life, re-establishing health or alleviating suffering”]
- **Question:** When is it **reasonable** for the physician to recommend an investigational drug with no proven safety and/or efficacy?

Assessing risk and benefits



[DiMesi et al. 2003]

Help, or at least do no harm!

- Risk-benefit profile of interventions unproven in humans in uncertain.
- Side-effects might be significant, much higher then expected benefits. There is also a danger of giving false hopes.

Threat to the integrity of the medical profession

- „As doctors, trying an untested drug on patients is a very difficult choice since our first priority is to do no harm, and we would not be sure that the experimental treatment would not do more harm than good" [Arie 2014: 4998]
- „Physicians have interest in maintaining the integrity of the medical profession that can counsel against offering patients any intervention that might have *some* chance of providing benefit" [Shah et al. 2015: 12]

Threat to the patients' trust in medical profession

Is it obligatory ?

***Rather*:**

Is it permissible, and if yes, under what conditions?

Ethical requirements

- There is strong evidence of safety & some evidence of effectiveness (**risk/benefit profile better than alternatives**)
- Patient suffers from life-threatening or seriously debilitating illness, and
- she has already exhausted all available therapeutic options.

Justification [2]

Respect for autonomy	**Respect for autonomy** – „right-to-try", „right-to-chance", [Dresser 2015]; „right to mitigate extreme suffering and to enhance self-preservation" [Darrow et al. 2015]
	Promotion of autonomy – more options for patients: RTC or CUP [Kodish 1991; Schuklenk 2016]

Respect for autonomy

„This logic holds that as rational actors, **patients are presumed to be capable of making well-informed treatment decisions** in consultation with their physicians. According to this argument, **not only can patients with serious or life-threatening conditions accurately identify promising experimental drugs, but they should also be entitled to utilize their own risk–benefit thresholds in deciding whether to consume such products”**. [Darrow et al. 2015: 283]

Problems

- **Vulnerability of the patients**
  - **Due to disease**: physical exhaustion, psychological distress, social isolation…
  - **Due to lack of registered therapeutic options**: risk of exploitation, particularly if they are charged for having access to experimental drugs
- No sufficient data to make a „well-informed" decision
- No time to make a deliberated choice.

Replies and ethical requirements

- [***Ad vulnerability***] Seriously ill patients are deemed capable of giving consent for participation in research, including trials to test new drugs, so they should also be deemed capable of giving consent to experimental treatment with unproven drugs outside research context.
- [***Ad risk of exploitation***] Compassionate use programs should offer experimental drugs free of charge.
- [***Ad quality of IC***] „measures should be taken to guarantee autonomy for patients. This means monitoring the quality and validity of informed consents given and being attentive to the possibility of excessive therapeutic optimism" [Raus 2016:7]

Justification [3]

Justice, fairness

Fair access to innovative / experimental drugs

Majority of seriously ill patients are excluded from participating in clinical trials due to factors outside of their control: „distance to the trial, the number of participants allowed in the trial, the condition on which the drug is tested, the patient's physical condition" [Raus 2016: 3]

But, only if compassionate use programs guarantee fairness in allocation of experimental drugs.

Fairness to future patients

- Compassionate use programs may cause delays in the initiation, conduct and completion of clinical research
  - depletion of investigational drug resources
  - problems with the patients recruitment
- *Ergo*, they may cause delays in the development of generalizable knowledge that could lead to the development of safe and effective treatments for future patients.

Compassionate use is compatible with learning

- Clinical use of unapproved drugs outside of the research context **should not preclude or delay the initiation of properly designed clinical studies**.
- **It is a moral obligation of physicians offering unproven interventions "to collect and share all the scientifically relevant data generated, including from treatments provided for compassionate use".**

*Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO; 2014

Conclusion

- No single ethical principle *per se* can provide an adequate justification for compassionate use programs.
- „If compassionate use is to be justified by reference to justice, beneficence and autonomy, measures must be taken to justify this reference” [Raus 2016: 9]

Parts of this talk were presented at:

- 30th European Conference on Philosophy of Medicine and Health Care (ESMPH), Zagreb, Croatia, 17-20 August 2016: invited talk: *Justifying risks of experimental interventions offered to Ebola patients outside the context of research.*
- Workshop *Ethical Challenges of Research Conducted in Disaster Settings*, organized by the Disaster Bioethics COST Action IS1201 and Jagiellonian University Medical College, Krakow, Poland, 8-9 February 2016: invited talk: *Ethics of using experimental Ebola treatments.*

Thank you

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