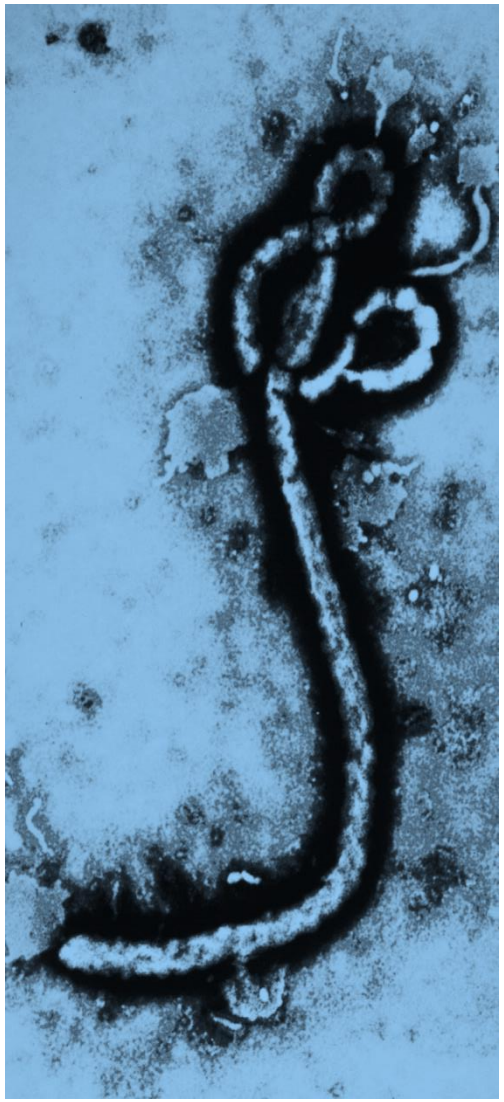


Ethics of using experimental Ebola treatments

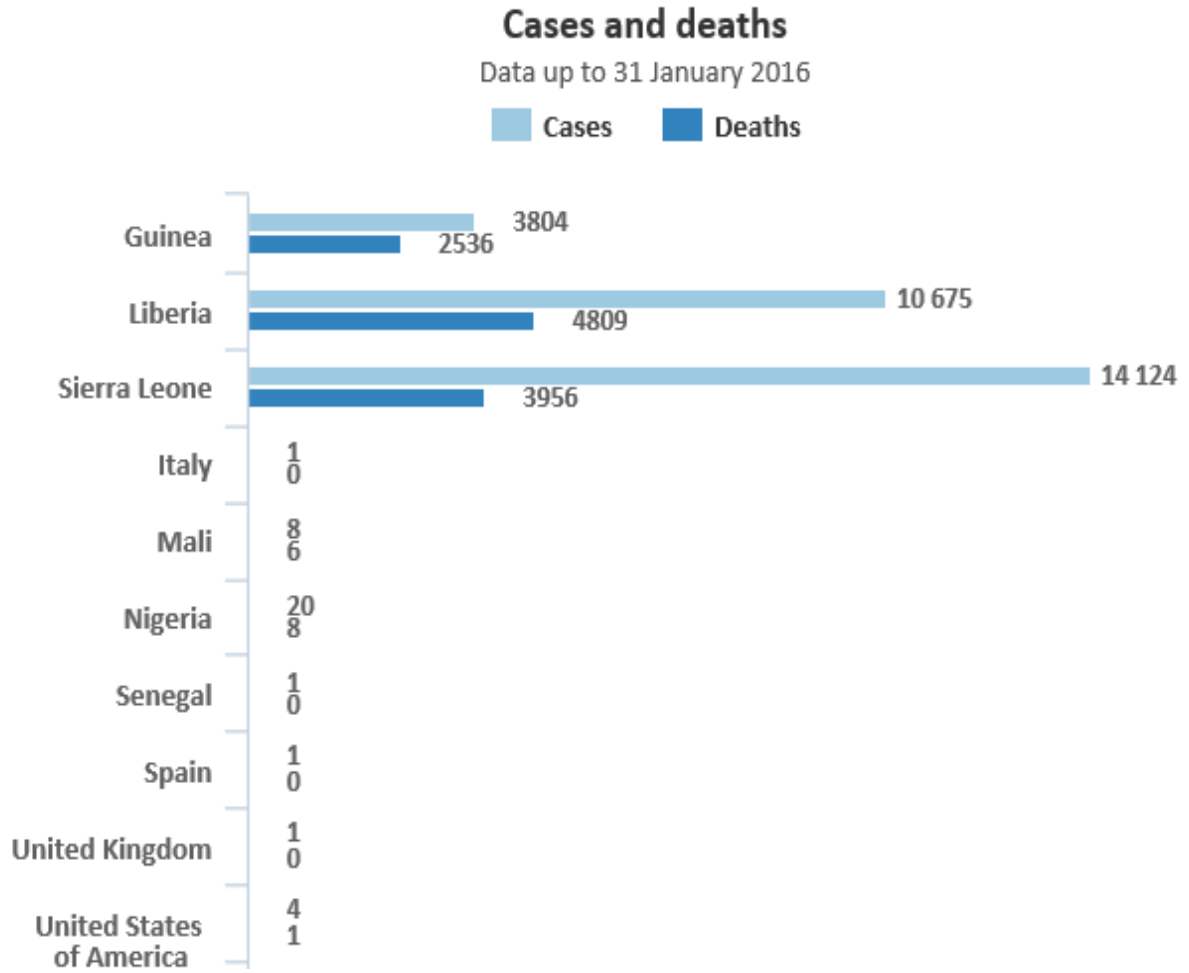
JOANNA ROZYNSKA, PhD

Center for Bioethics & Biolaw
University of Warsaw, Institute of Philosophy
Warsaw, Poland
www.cbb.uw.edu.pl j.rozynska@uw.edu.pl

Victims of EVD

- Since the onset of the Ebola outbreak in December 2013
  - **28 603** cases (confirmed, probable, and suspected)
  - **11 301** deaths

  have been reported in Guinea, Liberia, Sierra Leone, and othe countries.
- **Mortality rate: 55-70%**



http://apps.who.int/ebola/current-situation/ebola-situation-report-3-february-2016

Therapy & Prevention

- **There is no proven treatment available for EVD.**
- Only a few randomized controlled trials have been developed so far. Some of them have been already halted due to the lack of likelihood that they would demonstrate an overall therapeutic benefit; others are still in progress.
- Supportive care: rehydration with oral or intravenous fluids, and treatment of specific symptoms.
- No proven vaccines are available yet. [The VSV-EBOV vaccine (Merck, Sharp & Dohme) is highly promising]

Compassionate use

Given the very high mortality rate of the EVD and lack of treatment proven aside from supportive care,

several untested interventions have been administered to Ebola patients on a so called “compassionate use”, ”emergency use”, ”off-label use” or “expanded access program” basis.

World Health Organization

entre | Publications | Countries | Programmes | Governance | About WHO

Essential medicines and health products

Compassionate use of experimental treatments for Ebola virus disease: outcomes in 14 patients admitted from August to November, 2014.

Table 1: Specific combinations used

ZMapp	*Conv Plasma*	*siRNA*	*Favi-piravir*	*Brinci-dofovir*	*ZMAb*	
x						4
x	x					1
	x		x			1
		x	x		x	2
			x			2
			x	x		1
			x		x	1
Total (N patients receiving investigational treatment)						12

http://www.who.int/medicines/ebola-treatment/outcomes_experimental_therapies/en/

WHO Advisory Panel [2014]*

„Having considered the points above [stressing the urgent need to conduct scientifically sound and rigorous clinical studies], the **panel agreed unanimously that, in the exceptional situation of the current Ebola outbreak, there is an ethical imperative to offer the available experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease**, with the proviso that the conditions listed below are met."

*Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO; 2014: 5

WHO Advisory Panel [2014]*

The ethical criteria include:

- **transparency about all aspects of care**, so that maximum information is obtained about the effects of the interventions,
- **fair distribution in the face of scarcity**,
- **promotion of cosmopolitan solidarity**,
- **informed consent**, freedom of choice, confidentiality, respect for the person,
- **preservation of dignity and involvement of the community,**
- **the best possible assessment of risk and benefit** from the available information.

*Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO; 2014: 1, 5

WHO Advisory Panel [2014]*

- Clinical use of unapproved interventions 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

Questions

- What justifies compassionate use in Ebola emergency?
- Is it indeed ethically permissible/obligatory to offer unproven interventions to Ebola patients outside the context of research?

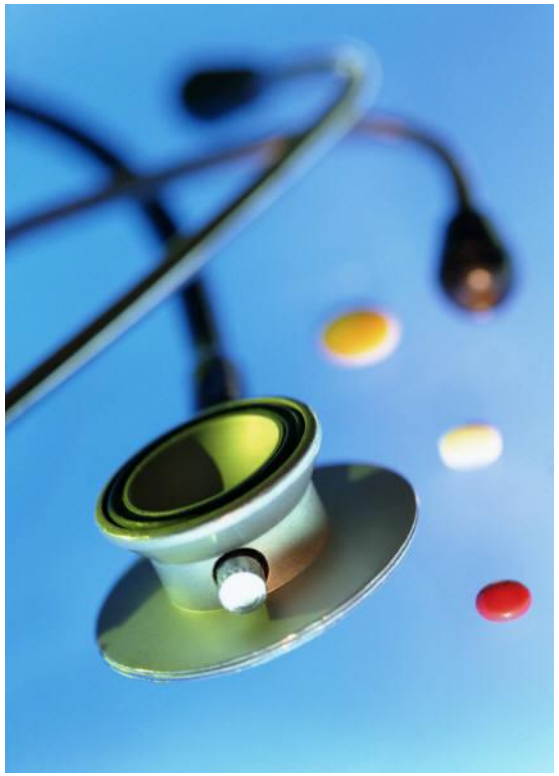
„Compassionate use is justified as an **exceptional emergency measure**. It should not preclude or delay the initiation of more conclusive investigations of the intervention in properly designed clinical studies. Under the current evolving circumstances, **no single ethical discourse can adequately capture all the issues that justify compassionate use, and no single principle or normative consideration is likely to supersede the others**".

*Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO; 2014: 1, 5-6

Exceptional number of victims?

- EVB is responsible for 11 301 deaths in 2014-2015.
- WHO estimates that globally:
  - Only in 2015, there were roughly 214 million malaria cases and an estimated **438 000 malaria deaths**.
  - Only in 2008, circa **453 000 child deaths** occurred due to rotavirus infection.
  - Annual influenza epidemics result in between 3 to 5 million cases of severe illness and between **250 000 and 500 000 deaths every year.**

Exceptionally dire?



- Patients with EVD have 30-45% chance of long-term survival, being provided only with supportive care.
- Patients in the last stage of an oncological disease, who have exhausted all available treatment options, have 0% chance of long-term survival.

Justification [1]

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

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 where there are no safe and effective measures to prevent the patient from harm?**

[Sheehan 2007; Rulli & Millum 2013]

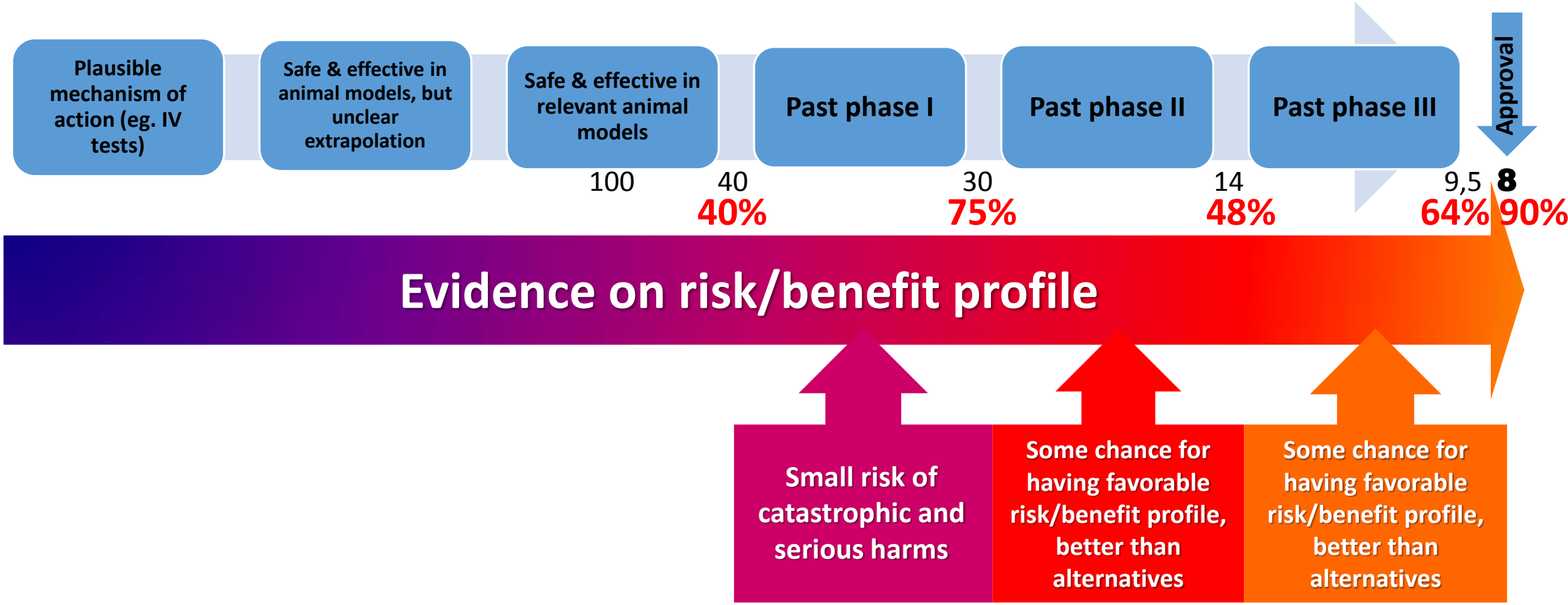
Professional duty to rescue/care

- The duty seems to actualize only when the physician **can help**, namely when there is solid evidence that a given intervention would benefit the patient.
- **Undoubtedly, the duty applies to standard care**; in case of the EVD – supportive care.
- BTW: Force and scope of the physician's special obligations to rescue/care during an infectious disease outbreak is a subject of on-going controversy [eg. Ruderman et al. 2006; Morin et al. 2006; Malm et al. 2008]

Clinical use of unproven interventions

- Clinical use of unproven interventions (esp. in the first-in-human setting) 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 intervention 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 patients' 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?

Compassion

- What is compassion? What is its normative force and scope?
  - 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
- Maybe it is just a „label” for the mixture of different psychological phenomena, such as apathy & egoistic fear; hope & panic; sense of obligation towards others & wish to push the danger away…

Justification [2]

Respect for persons	**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]
	Primacy of the human being [*indirect argument against placebo controlled RCTs*]

Limited autonomy of the Ebola patient

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]

- **Vulnerability of the patients**
  - Due to disease: physical exhaustion, psychological distress, social isolation
  - Socio-economic status
- No sufficient data to make a „well-informed" decision
- No time or/and intellectual capacity to make a deliberated choice.

Primacy of the human being

Declaration of Helsinki (2013)	• While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects. (Par. 8)
Oviedo Convention (1997); Additional Protocol on Biomedical Research (2005)	• **The interests and welfare of the human being shall prevail over the sole interest of society or science**. (Convention - Art. 2) • The interests and welfare of the human being participating in research shall prevail over the sole interest of society or science (Additional Protocol - Art. 3)
Universal Declaration on Bioethics and Human Rights (2005)	• **The interests and welfare of the individual should have priority over the sole interests of science or society** (Art. 3 par. 2)

Instrumentalisation of the Ebola victims

- This is an argument against the position to offer experimental interventions only in clinical trails – RCTs with placebo control [Joffe 2014; Cox et al. 2014; Rid & Emanuel 2014]
- It is unethical to randomize patients with a disease that has a 55%-70% fatality rate to a control placebo group when an intervention that holds any promise for reducing the risk of death is available.

„Such randomisation is ethical when there is equipoise—when there is genuine uncertainty about whether an untested treatment has benefits or risks that exceed those of conventional care. Equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high. This is precisely the problem with Ebola…. **When conventional care means such a high probability of death, it is problematic to insist on randomising patients to it when the intervention arm holds out at least the possibility of benefit**."
[Adebamowo et al. 2014: 1423; also Edwards 2013]

Possible replies

- Given an uncertainty of therapeutic potential of a new intervention, there **might be a genuine uncertainty** *ergo* clinical equipoise.
- Supply of investigational interventions against Ebola has been extremely limited. **Only few patients in would have a chance to try it**. Thus, patients-subjects randomized to the placebo arm, would not have been worse off or treated instrumentally.
- If we still believe that randomization and use of placebo control is unethical, we may try to use **alternative more flexible, adaptive research designs** [Adebamowo et al. 2014] or cluster or wedged cluster trials [Edwards 2013] which will allow for combining research with care.

Rationale [3]: Compassionate use is compatible with learning

- Clinical use of unapproved interventions 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

Let's be realistic!

- Data collection is difficult in expanded access and may be impossible during an epidemic due to general chaos, panic, mistrust, decay of infrastructure, medical professionals sickness, etc.

„This update presents data on 14 individuals with laboratory-confirmed Ebola who were treated with experimental therapies and/or in high-income settings during the 2014 outbreak. Mortality was considerably lower among these patients, compared with Ebola patients treated in West Africa. **As expected, the large variety of treatment modalities used and the small numbers of deaths preclude any meaningful conclusions about association between use of specific experimental treatments and mortality**. Clinical trials currently being conducted in West-Africa will hopefully provide definitive answers on the efficacy of the treatments"

Compassionate use and scare resources

- Delays in the initiation, conduct and completion of clinical trials
  - depletion of investigational drug resources
  - problems with the patients recruitment
- Delays in the development of generalizable knowledge that could lead to the development of safe and effective treatments for future patients.

Conclusion

What makes offering an experimental intervention that have shown promising results in the laboratory and in relevant animal model to Ebola patients an **ethical imperative?**

Justification/rationale	
Duty to rescue	N Only if reasonable in the light of available evidence
Duty to care	
Compassion	?
Respect for autonomy	N
Primacy of the human being	N
Compatible with research	N

Thank you

JOANNA ROZYNSKA, PHD

Center for Bioethics & Biolaw
Institute of Philosophy
University of Warsaw
Warsaw, Poland
www.cbb.uw.edu.pl
j.rozynska@uw.edu.pl