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MEDECINS SANS FRONTIERES
ÄRZTE OHNE GRENZEN
Unité de Recherche sur les Enjeux et Pratiques Humanitaires

Ethics of clinical trials in epidemic disasters

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philippe.calain@geneva.msf.org

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Benefit sharing: which communities?

Natural reservoir (fruit bats?) → Primates → Community outbreak → Nosocomial transmission

Bioterrorism!

Laboratory accident

Cross-border spread (rare until 2014)

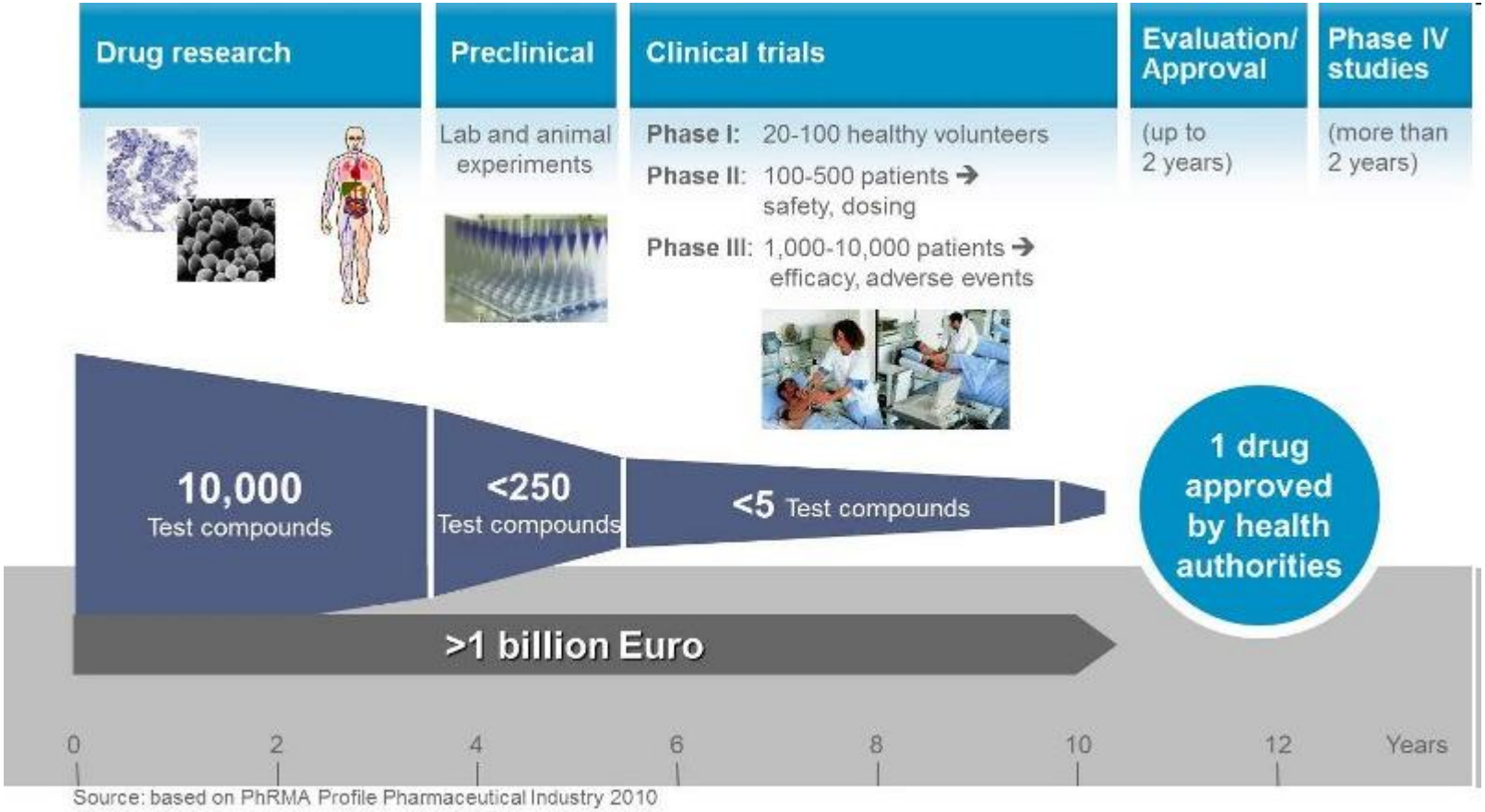
Drug clinical trials for Ebola, 2014 - 2015

Product	Phase	Trial Location
Favipiravir	Phase II	By INSERM in Guinea: Conakry, Guéckedou, Macenta, Nzérékoré
TKM-100802 (siRNA)	Phase II	By Oxford University in Kerry Town, Sierra Leone
ZMapp	Phase II	By NIAID in Liberia, Sierra Leone and the USA
Brincidofovir	Phase II	By Oxford University at the ELWA 3 Clinic, Monrovia, Liberia
Interferons	Phase II	By Guinea MOH in Coyah, Guinea
MIL-77	Phase I	Used in two expatriates under compassionate use. IND for phase I filed in China.
BCX-4430	Phase I	By Quotient Clinic in the UK

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

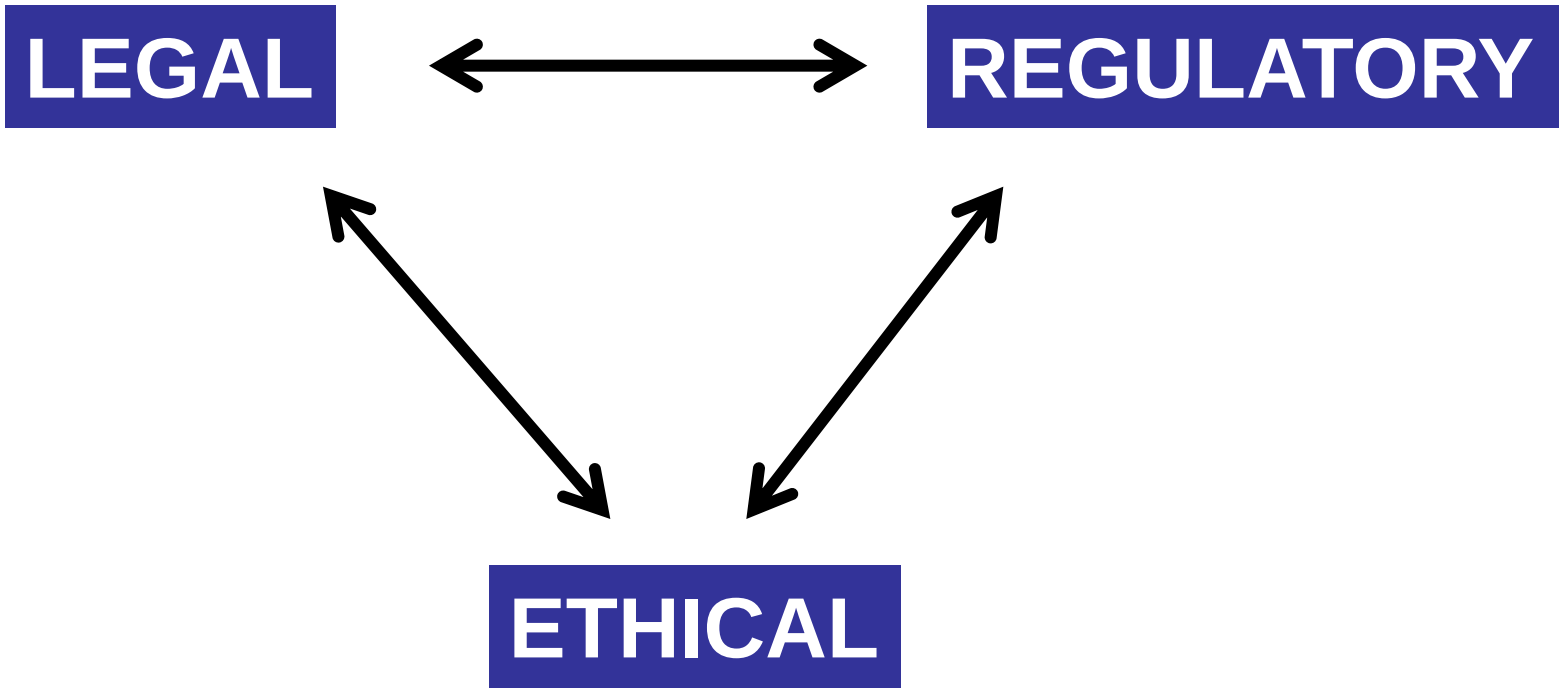
"Human clinical trials start in six months.
Sooner if we run out of mice."

Drug research and development



http://www.bayerpharma.com/en/research-and-development/processes/index.php

Oversight of pharmaceutical research and development



Ethical considerations for use of unregistered interventions for Ebola viral disease. WHO 11 August 2014.

‘*In the particular context of the current Ebola outbreak in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention*.’

An open agenda

1. Exceptional circumstances
2. Unproven interventions
3. Assumption: altruism and equipoise
4. Trial designs
5. “Compassionate” use

1. Exceptional circumstances

- Magnitude of the epidemic and its acute course?
- High lethality of EVD?
- Contagiousness?
- Actual or anticipated social disruptions?
- Additional burdens on deficient health systems?
- Or the concurrence of all those elements?

The Telegraph

If it works for Ebola, it can work for cancer

A new Bill will, in desperate cases, allow doctors to experiment with untested drugs

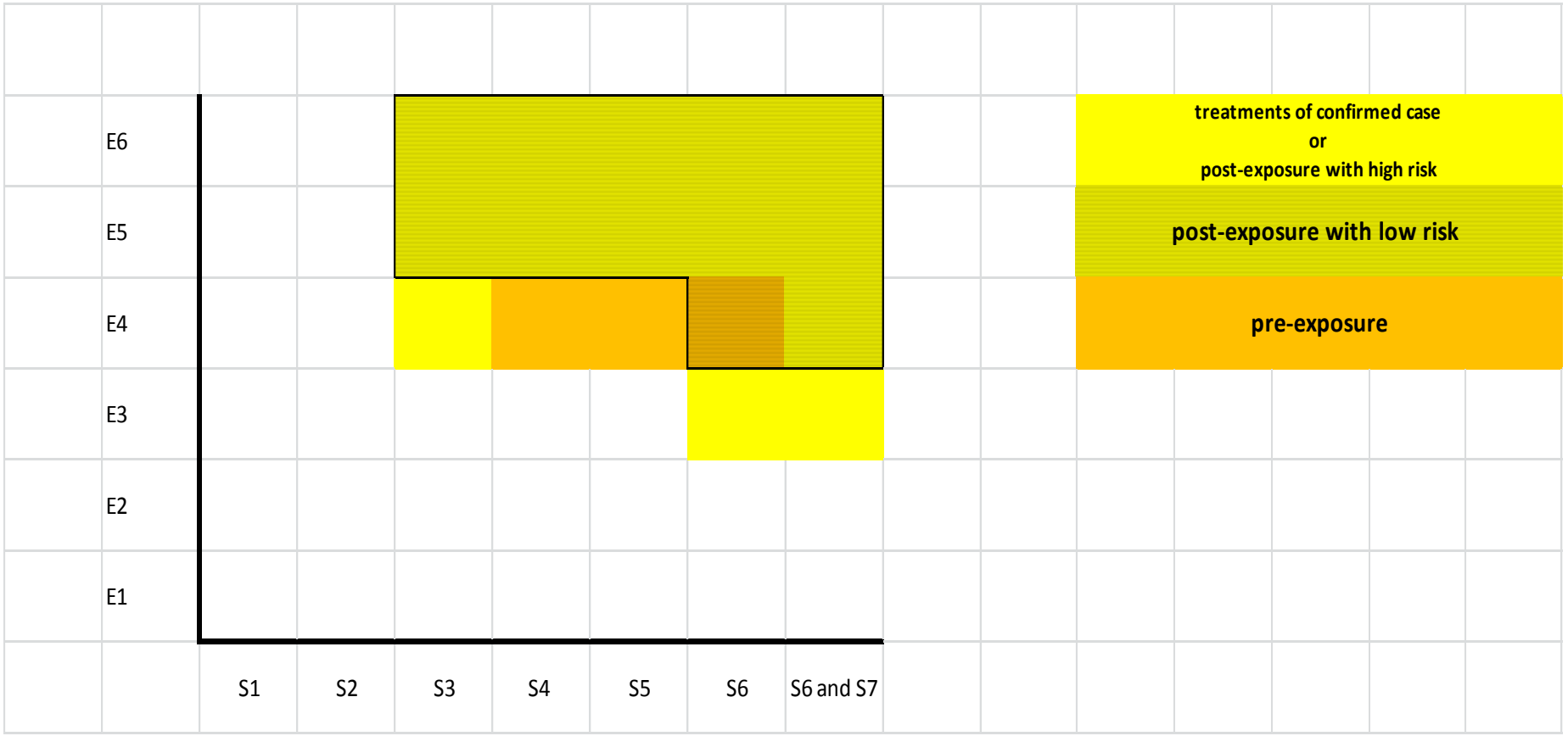
Maurice Saatchi has been fighting to improve cancer care following the death of his wife, Josephine Hart Photo: Rex Features

2. Unproven interventions

Past phase II	Past phase I	Safe and effective in relevant animal models	Safe and effective in animal models but unclear extrapolation	Safe and effective in relevant animal models/ repurposed drugs	No evidence to support use, but some reason to offer (e.g., plausible mechanism of action)

Shah SK, Wendler D, Danis M. Examining the ethics of clinical use of unproven interventions outside of clinical trials during the Ebola epidemic. Am J Bioeth. 2015;15(4):11-16.

2. Unproven interventions: risk/benefit



3. Wrong assumptions

ALTRUISM
“Patients primarily enroll in therapeutic trials for the sake of advancing collective knowledge and benefiting future generations”

CLINICAL EQUIPOISE
“There is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment.”

4. Controversies over (placebo-) randomized trials

4. Controversies over adapted trial designs vs. (placebo-) randomized trials

- Methodological

The supremacy of the placebo randomized trial as the most valid source of experimental knowledge is being challenged by the existence of equally robust designs

- Cognitive

The concept of randomization and its consequences are unlikely to be grasped by acutely patients in the midst of an epidemic.

- Moral

For clinicians attending Ebola-infected patients, randomization can thus be felt as a tragic choice, amounting to deliberately condemn half of their patients to possible harms, or to withholding possible live saving benefits.

5. ‘Compassionate’ use

Compassionate use (‘Expanded access’)

- typically refers to agents being evaluated in clinical trials, and for which some prior data on safety in humans exist.

- does not necessarily entail moral obligations to contribute to evaluating effectiveness.

MEURI

- ‘Monitored emergency use of unregistered and experimental intervention’

Ethical considerations for use of unregistered interventions for Ebola viral disease. WHO 11 August 2014.

‘*Capacity should be available to administer the experimental therapy in conjunction with the necessary supportive treatment, to monitor and manage any side-effects and to monitor the progress of treatment, including, at a minimum, measuring when possible appropriate surrogate outcomes, such as disease and immune response markers*’.

Conclusions

- New solutions but also many unresolved problems
- Emergency clinical trials in the course of a major epidemic represent rare opportunities to collect empirical data about the process of ethics oversight, and other critical questions of ethical relevance.
- Ethicists and social scientists should bring the voice of victims in an ethical debate that has too often been disembodied and rhetorical.