Risk/Benefit Evaluation in FIH Trials:
implications for gene editing in human embryos

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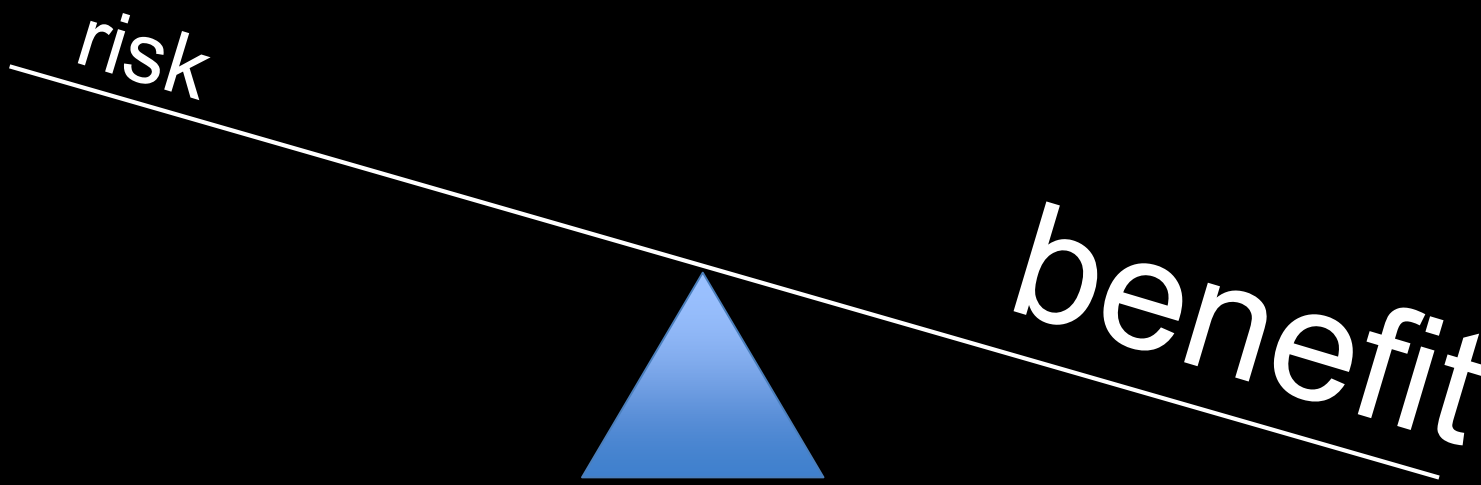

risk
benefit

?

part 1:
overview

part 2:
framework

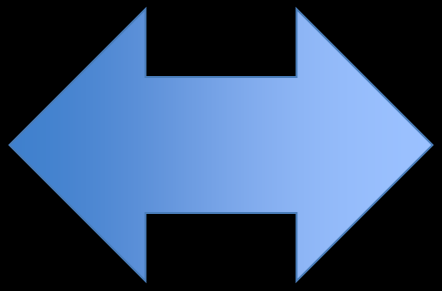
part 3:
extending to embryos

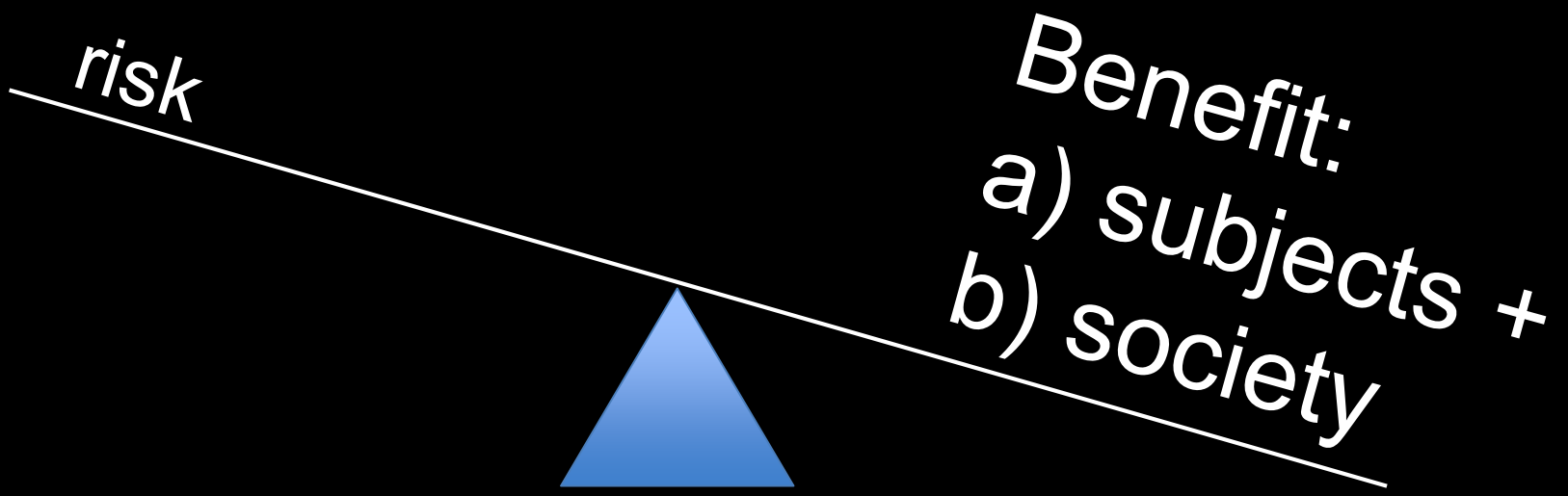
part 1:
overview

2

1) prior evidence

2) trial design

(1)  (2)

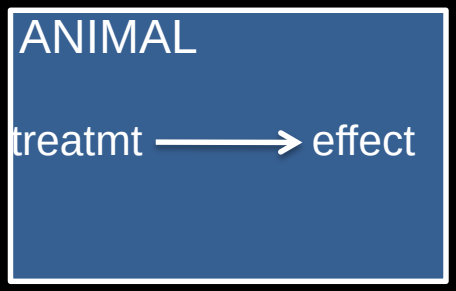

risk
Benefit:
a) subjects +
b) society

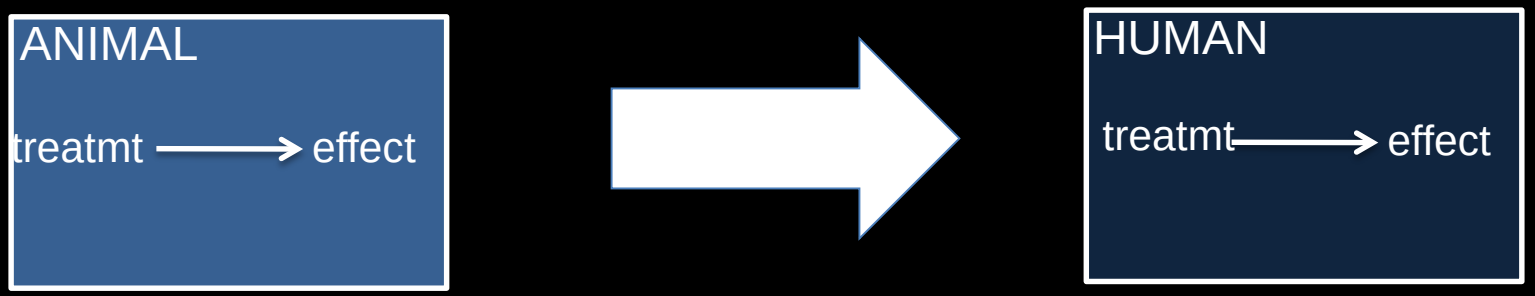
clinical promise

part 2:
framework

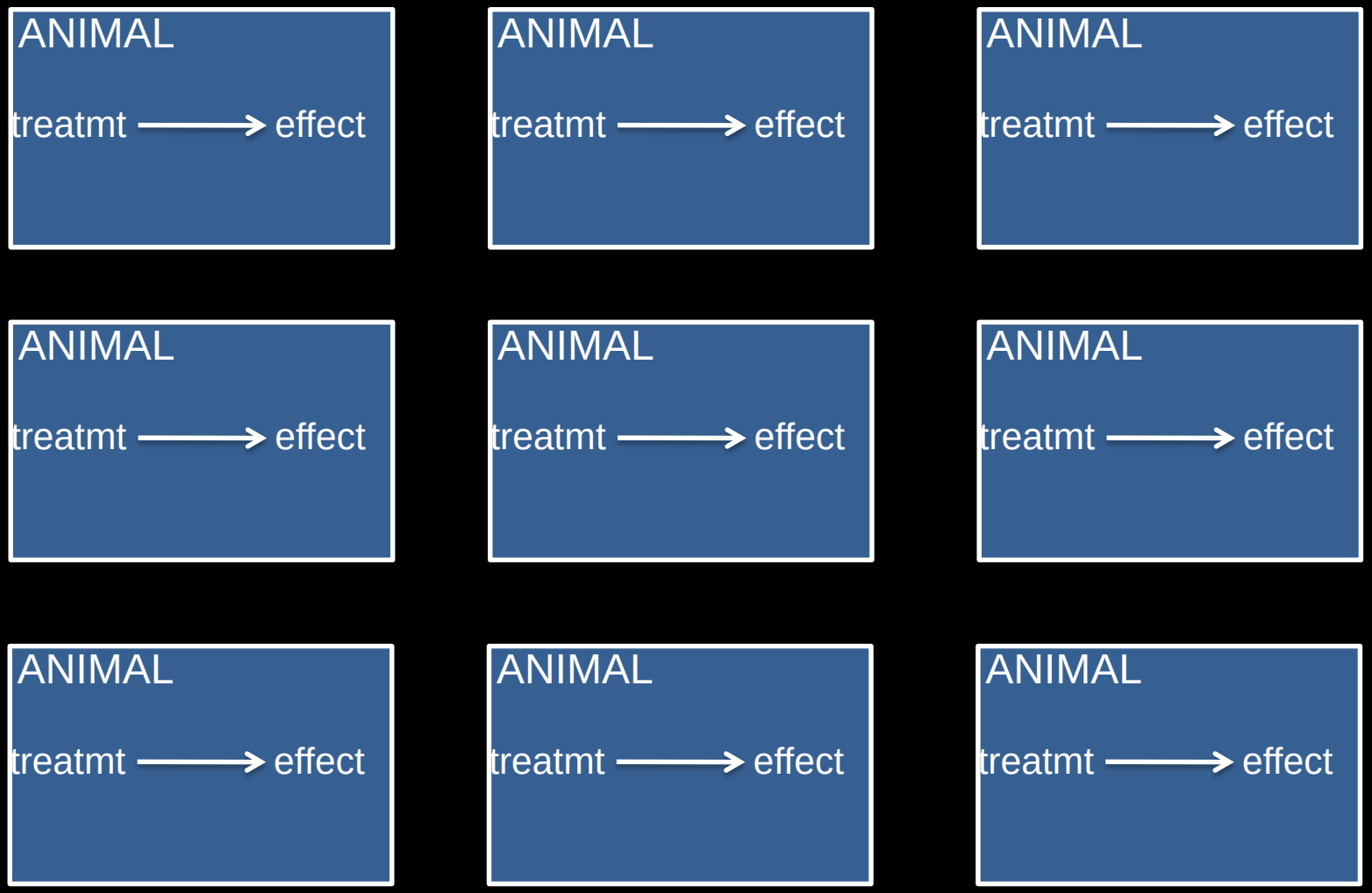
2

1. animal efficacy evidence


ANIMAL
treatmt
effect


ANIMAL
treatmt
effect
HUMAN
treatmt
effect

a)


ANIMAL
treatmt
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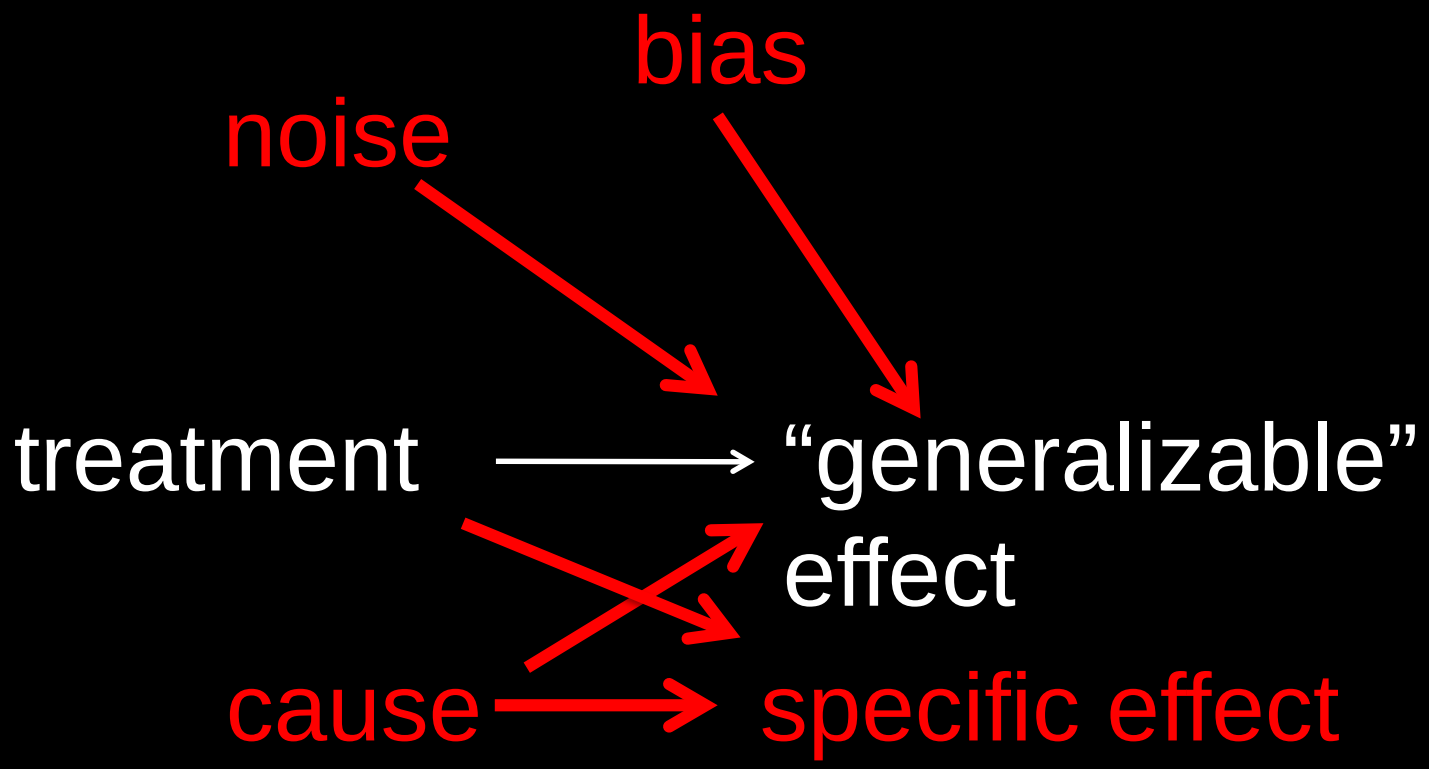
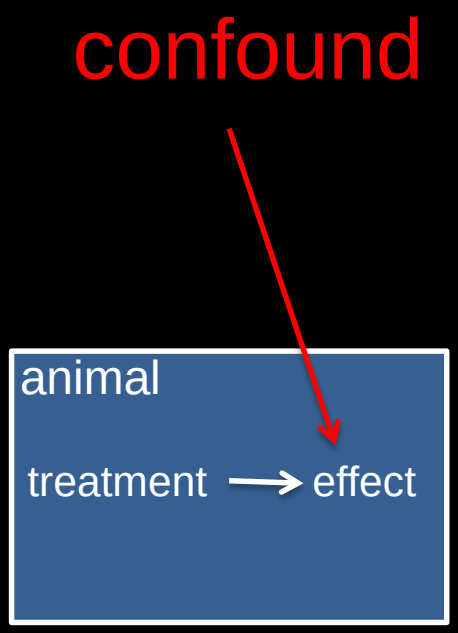
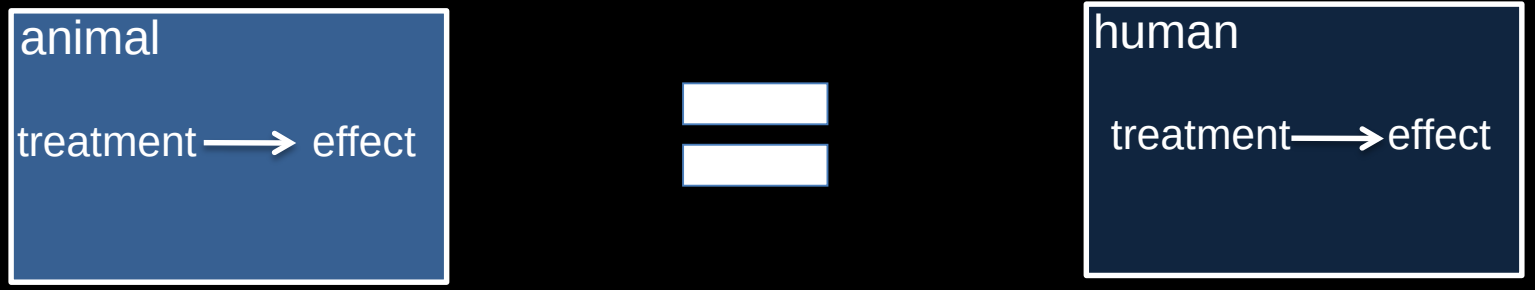
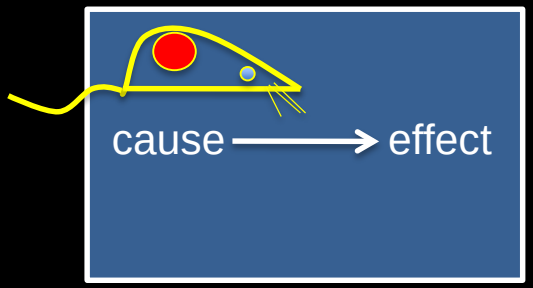
ANIMAL
treatmt
effect

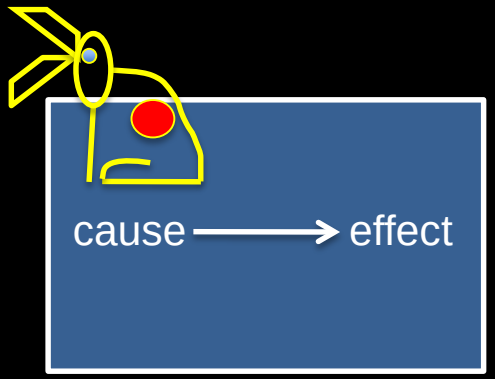
b)

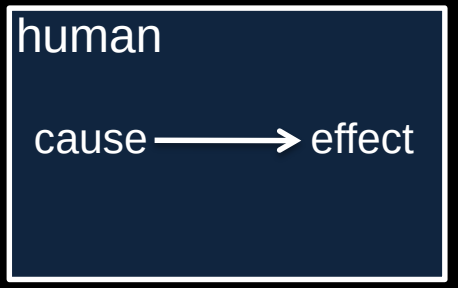

bias
noise
treatment
“generalizable”
effect
cause
specific effect

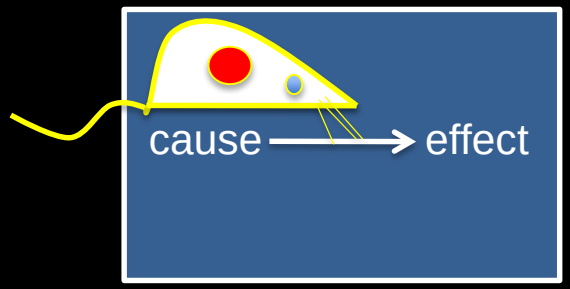

confound
animal
treatment
effect


animal
treatment
effect
=
human
treatment
effect


cause
effect


cause
effect


human
cause
effect


cause
effect

context specific

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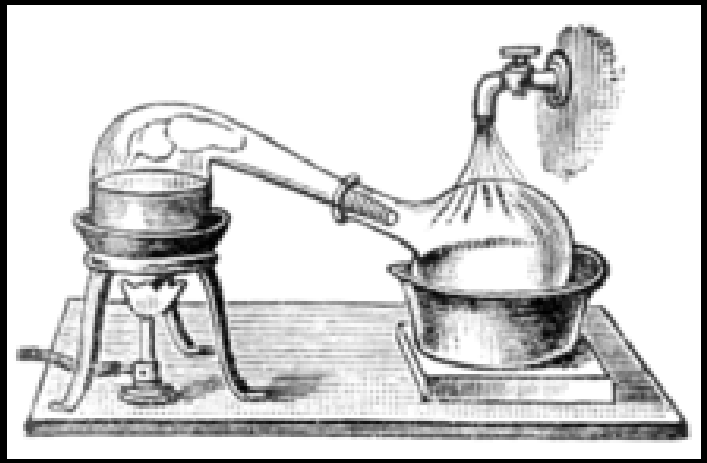
PLOS | MEDICINE

Threats to Validity in the Design and Conduct of Preclinical Efficacy Studies: A Systematic Review of Guidelines for In Vivo Animal Experiments

Valerie C. Henderson[1], Jonathan Kimmelman[1]*, Dean Fergusson[2,3], Jeremy M. Grimshaw[2,3], Dan G. Hackam[4]

PLoS Medicine 2013



Validity Type	Recommendation Category
Internal	Choice of sample size
	Randomized allocation of animals to treatment
	Blinding of outcome assessment
	Flow of animals through an experiment
	Selection of appropriate control groups
	Study of dose–response relationships
Construct	Characterization of animal properties at baseline
	Matching model to human manifestation of the disease
	Treatment response along mechanistic pathway
	Matching outcome measure to clinical setting
	Matching model to age of patients in clinical setting
External	Replication in different models of the same disease
	Independent replication
	Replication in different species

2. clinical evidence

reference class

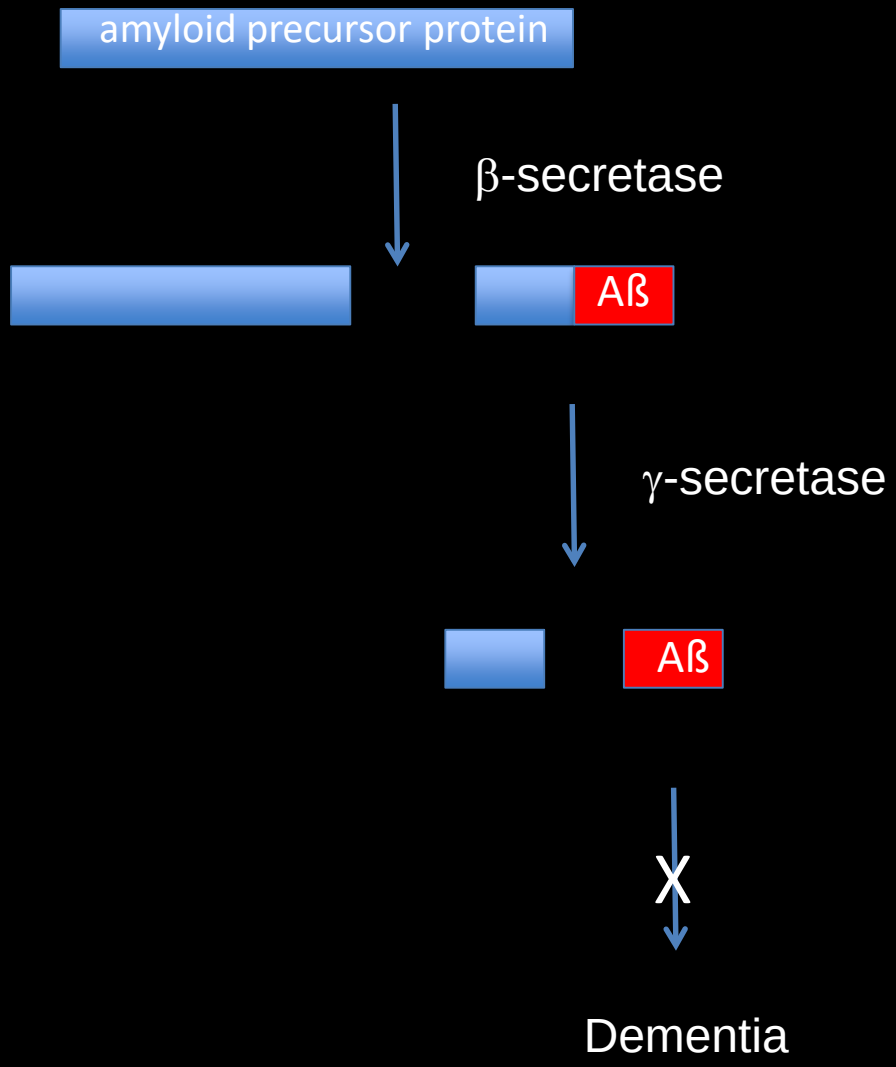

amyloid precursor protein
β-secretase
Aß
γ-secretase
Aß
X
Dementia

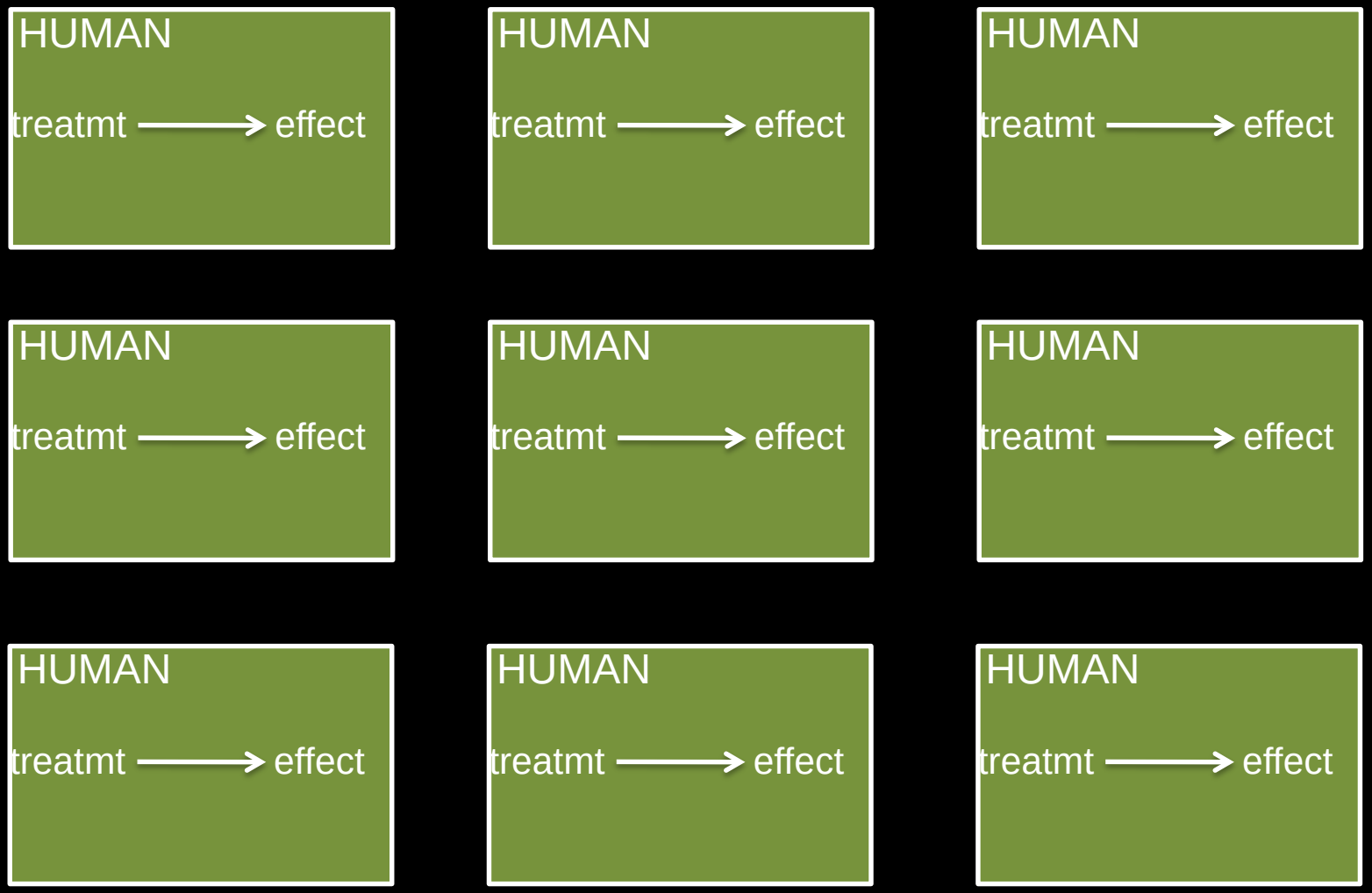
Table 1: Outcomes in randomized trials of anti-amyloid drug candidates for Alzheimer's Disease

Drug	Phase	Outcome	Source
AN1792	2a	unacceptable toxicity	[34]
Atorvastatin	3	no significance vs. placebo for two co-1° endpoints	[35]
AZD-103	2	no significance vs. placebo for two co-1° endpoints; toxicity	[36]
Bapineuzumab	2	no significance vs. placebo for 1° endpoint	[37]
Phenserine	3	no significance vs. placebo in efficacy analysis	[38]
Rosiglitiazone	3	no significance vs. placebo for two co-1° endpoints	[39]
Tarenflurbil	3	no significance vs. placebo for two co-1° endpoints	[40]
Tramiprostate	3	no significance vs. placebo for 1° endpoints	[41]

∴ ↓ confidence

Source: Kimmelman J, London AJ, *PLoS Med 2010*

a)


HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect
HUMAN
treatmt → effect

b)

$p(RC)$

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Essay

Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty

Jonathan Kimmelman[1], Alex John London[2]*

1 Biomedical Ethics Unit, Department of Social Studies of Medicine, McGill University, Montreal, Quebec, Canada, **2** Department of Philosophy, Carnegie Mellon University, Pittsburgh, Pennsylvania, United States of America

PLoS Medicine 2011

b)

$$p(Eff^{rc}) \times p(Eff^{pc})$$

3. moral evaluation

- risk / benefit
- direct social value
- fecundity…

part 3:
extending to embryos

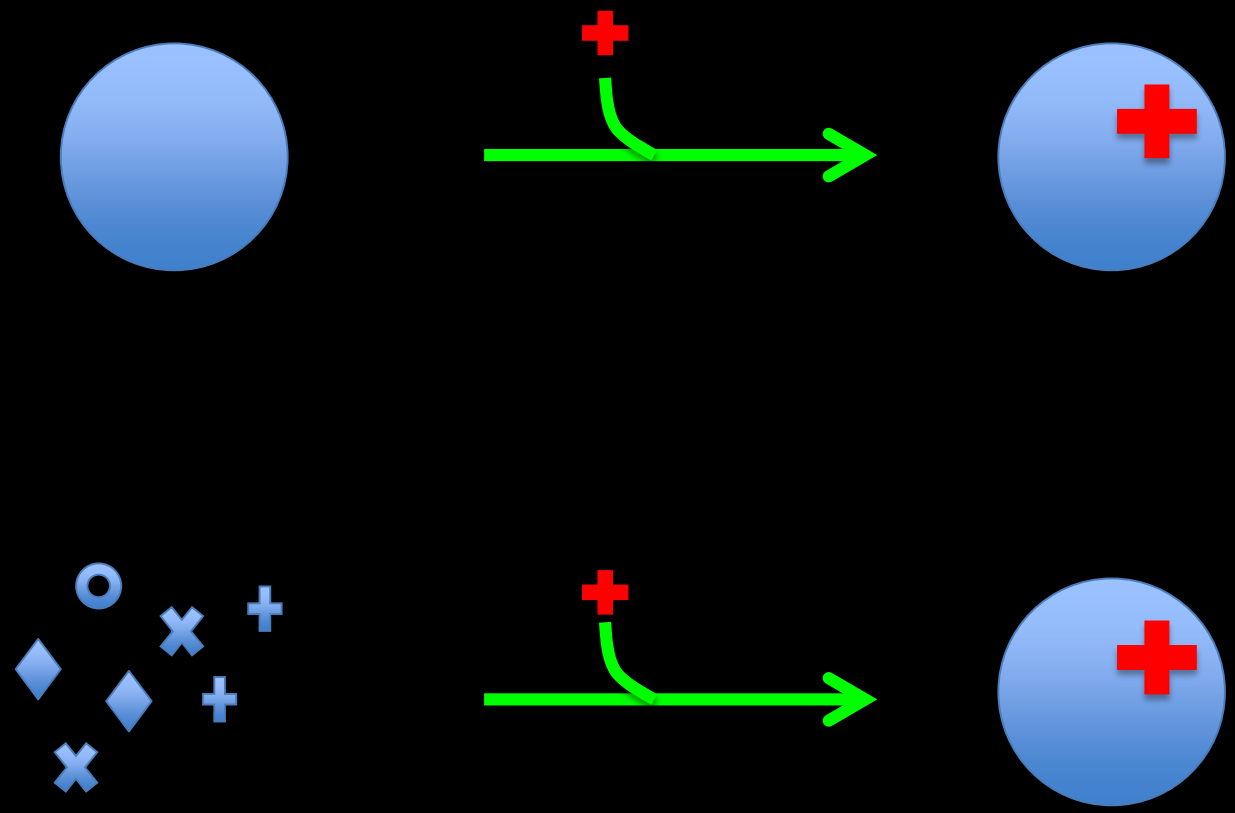
4

1. safety, not efficacy

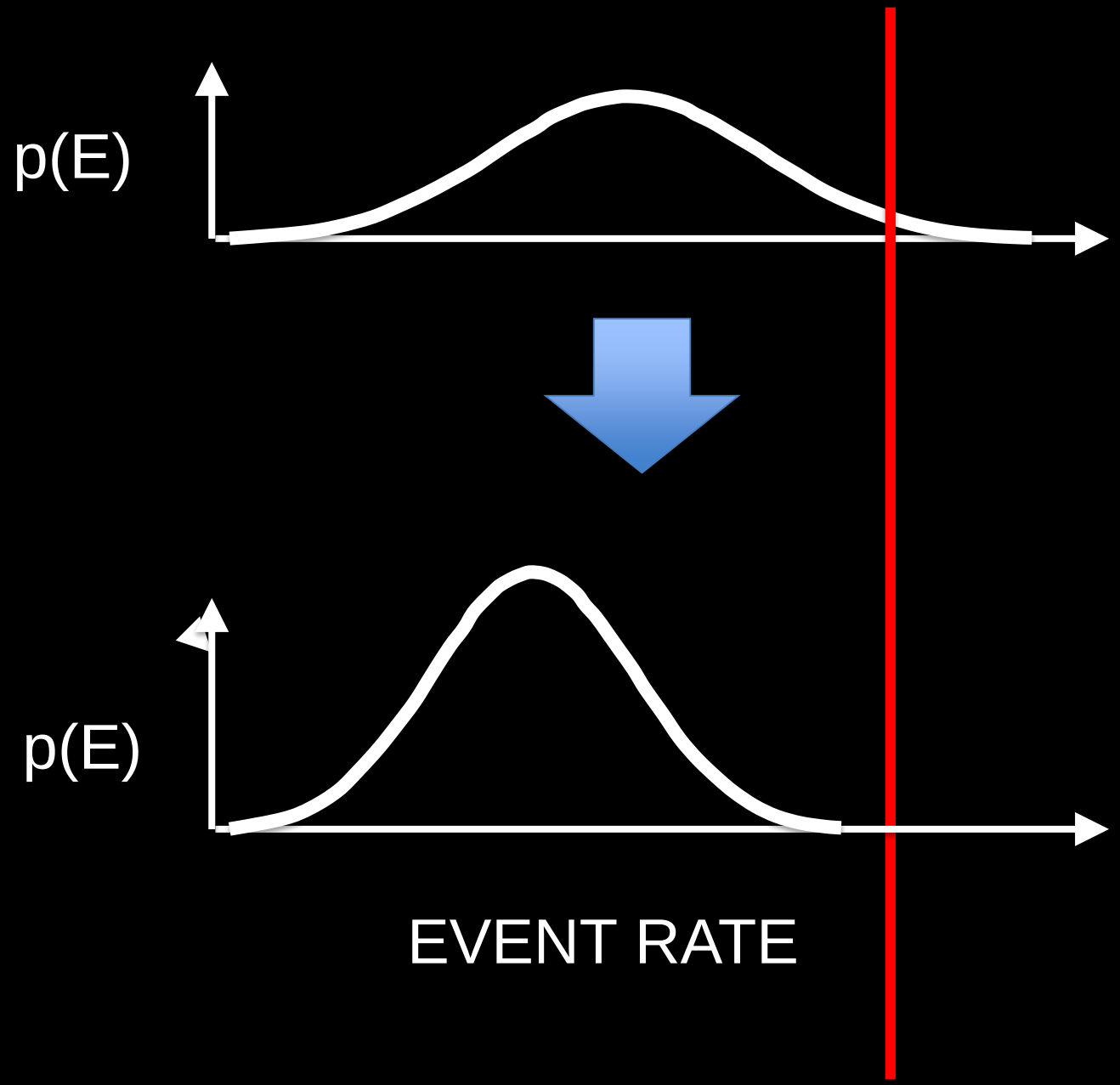
2. reference class

1st generation:
integrating vectors into pluripotent cells?

3. identity



4. long tail


p(E)
p(E)
EVENT RATE