

# Ethics and Early Phase Trials in Neurological Drug Development

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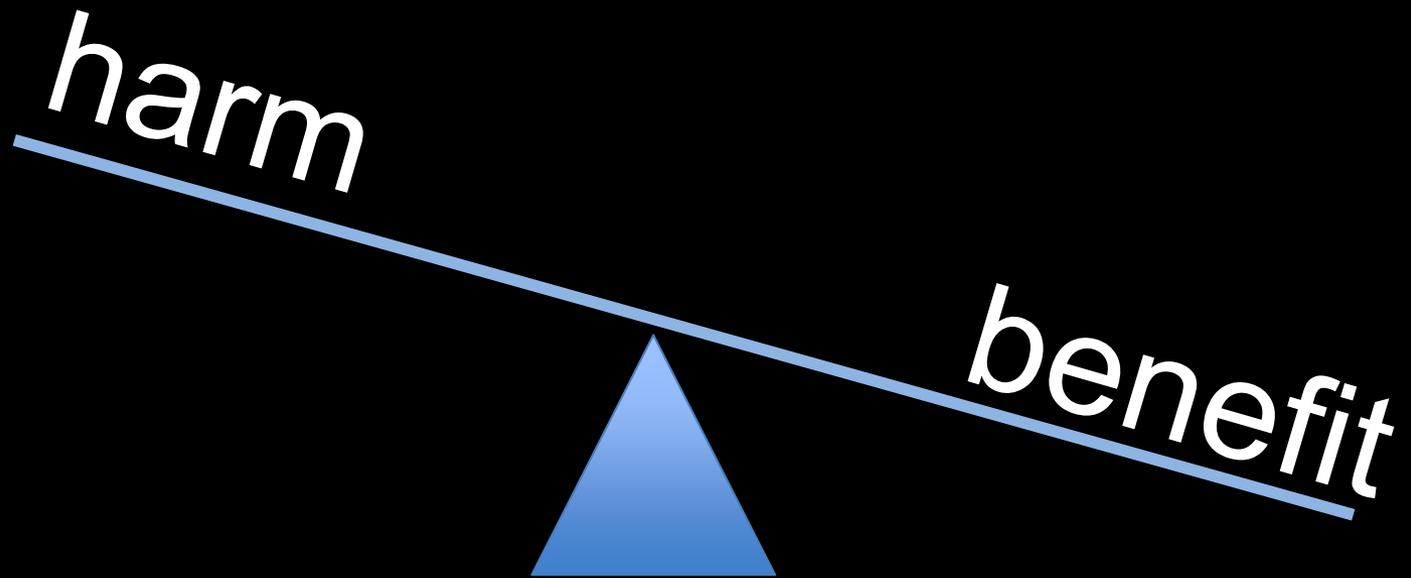


**STREAM**

Studies of Translation, Ethics and Medicine

6

1: establishing an ethical basis for trials requires engaging preclinical evidence

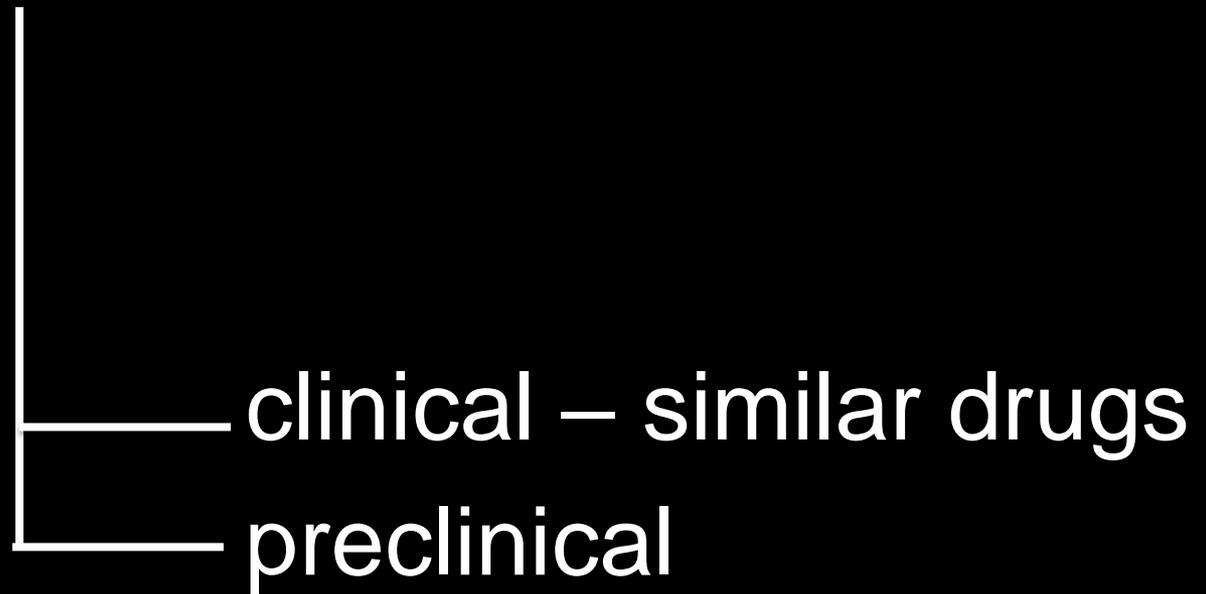


benefit  $\sim$  p(clinical app)

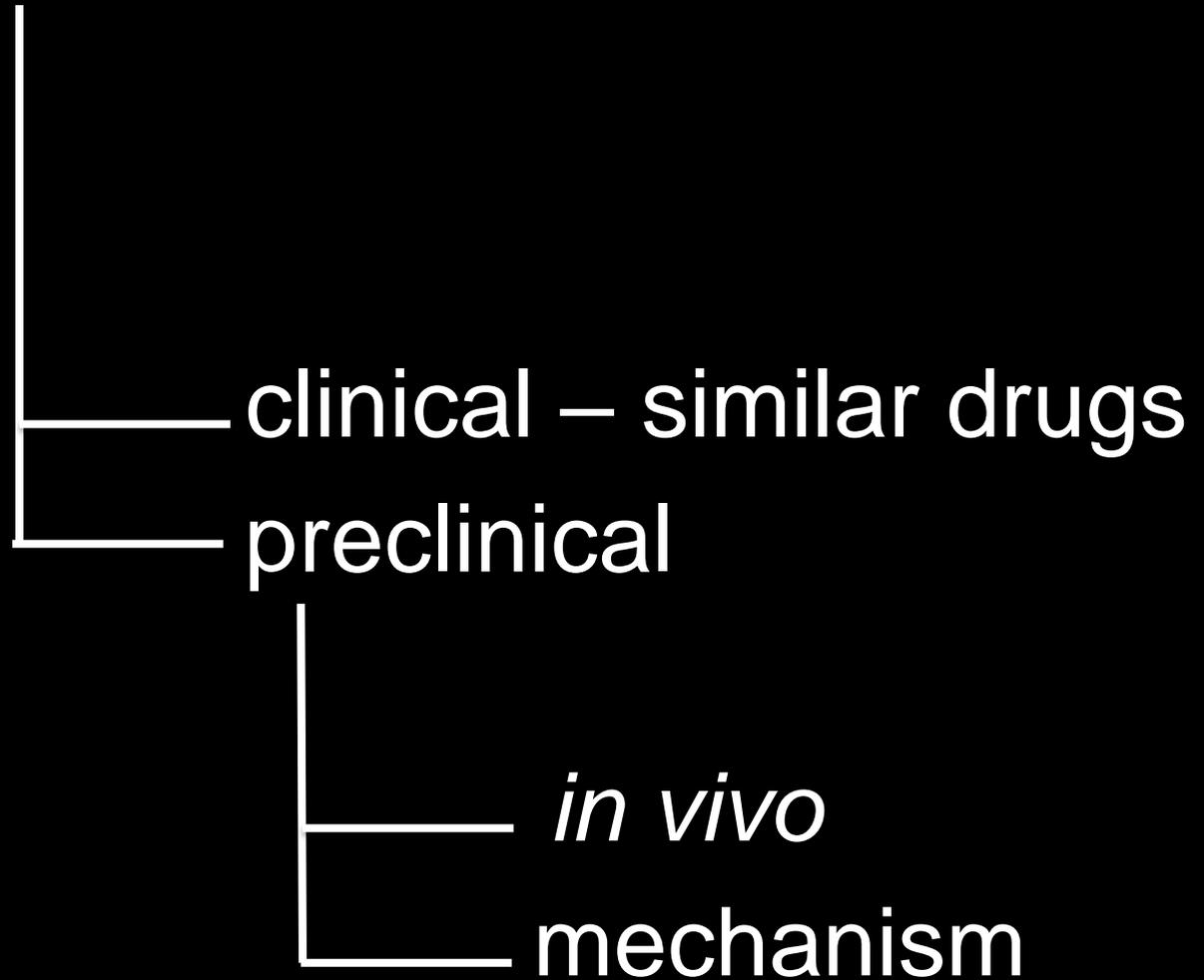
benefit  $\sim$  p(clinical app)

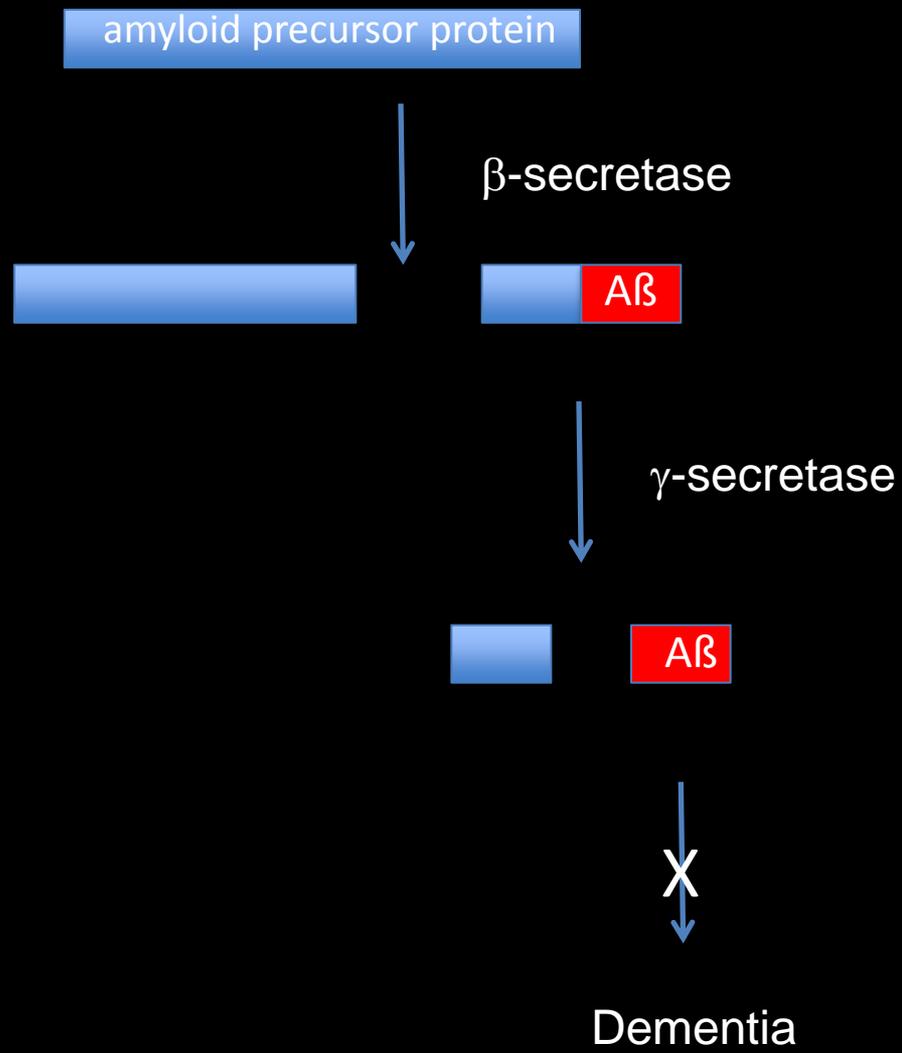
└── clinical – similar drugs

benefit  $\sim$  p(clinical app)



benefit  $\sim$  p(clinical app)





maximum  
uncertainty

shot in dark

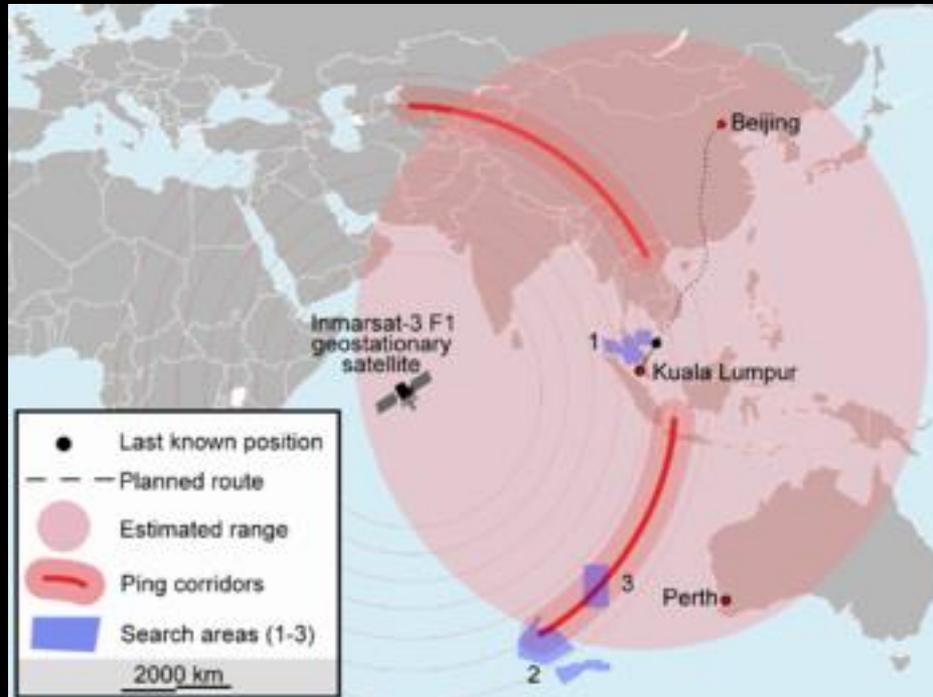
- $p(+)$  v. low
- if (-) little learned

shot in dark

- $p(+)$  v. low
- if (-) little learned

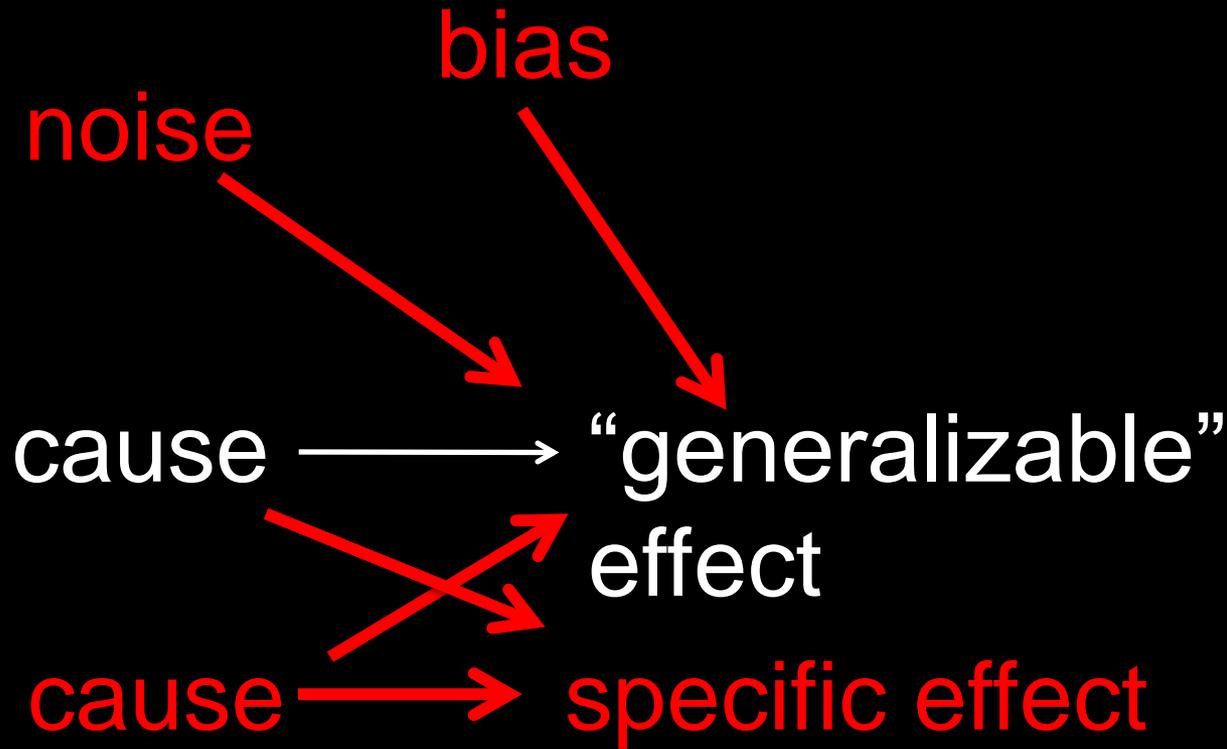
well-founded  
hypothesis

- $p(+)$  higher
- if (-) lots learned

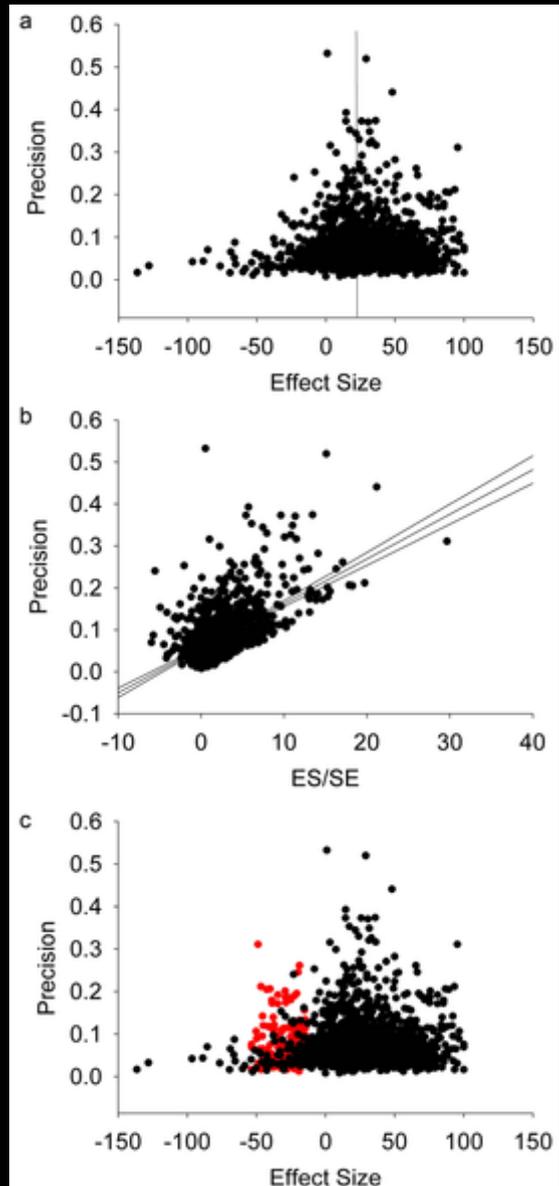


*fast & frugal*

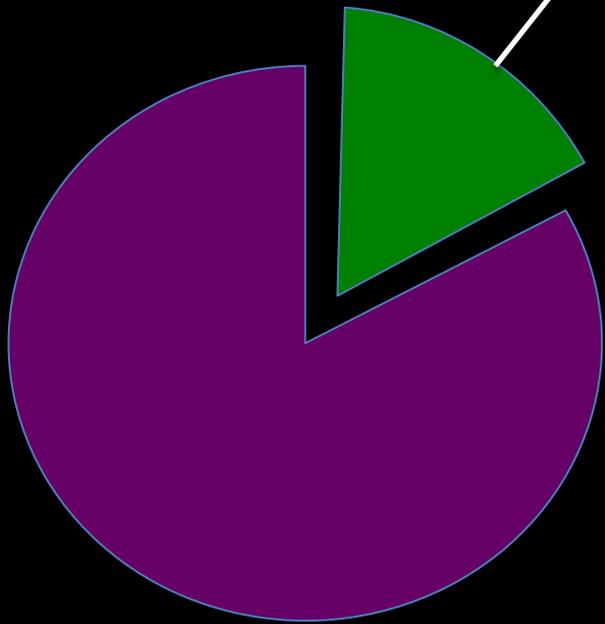
2: we are probably underutilizing  
preclinical evidence



little prespecification



replicated



useless <OR> misutilized

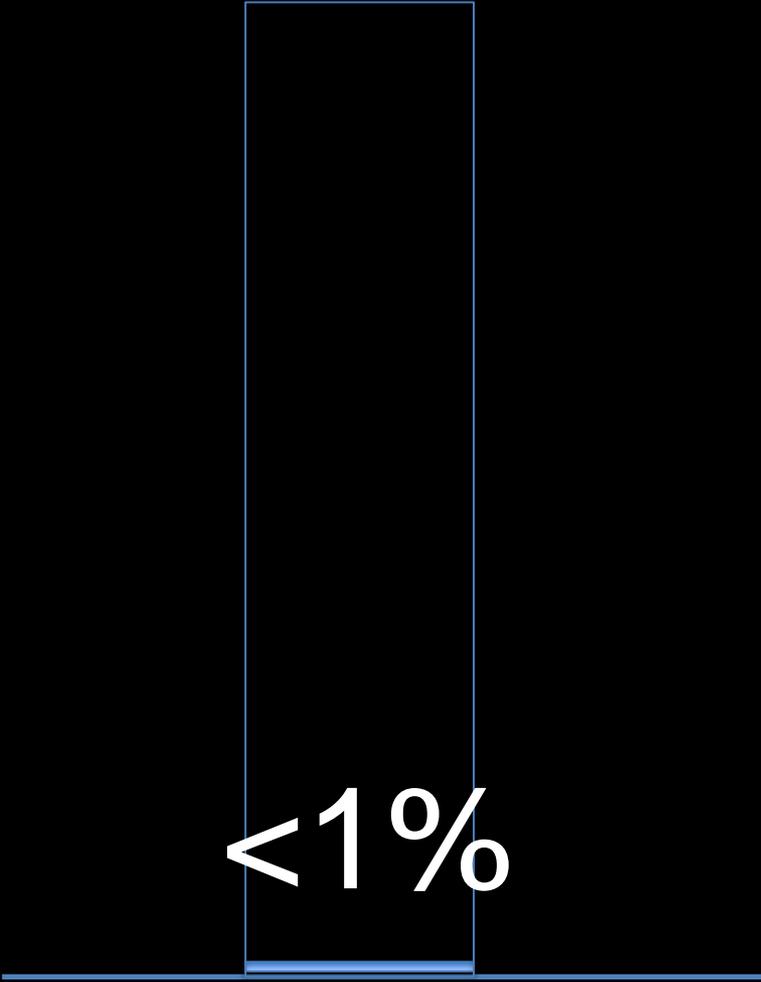
3: human protections for persons  
lacking competence do not  
make sense WRT early phase

- minimal risk
- minor increase > minimal
- therapeutic

~~• minimal risk~~

~~• minor increase > minimal~~

• therapeutic



A bar chart with a single bar. The bar is very short, representing a value less than 1%. The text "<1%" is written in white inside the bar. The bar is outlined in white and sits on a horizontal blue line. The background is black.

<1%

drug +

co-interventions

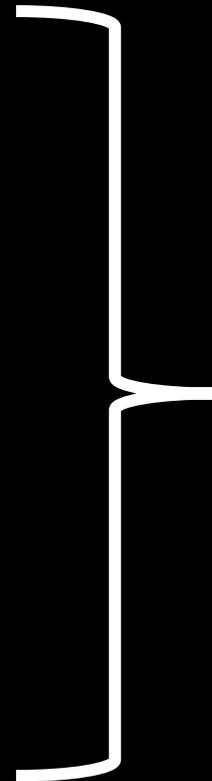
dose

schedule

diagnosis

monitoring

side effect mgmt

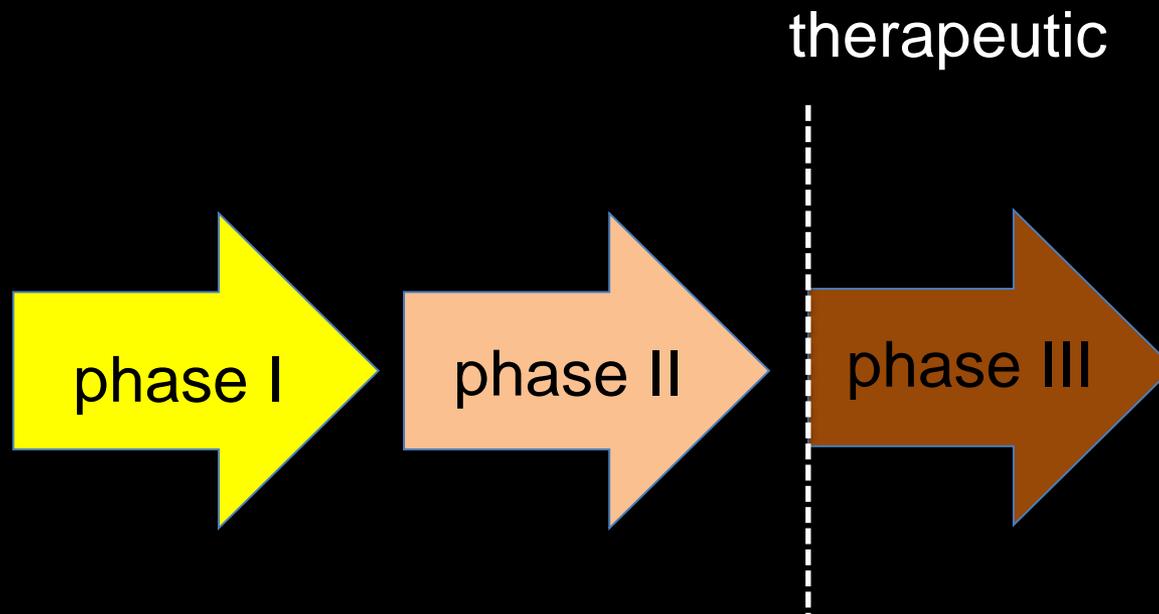


therapy

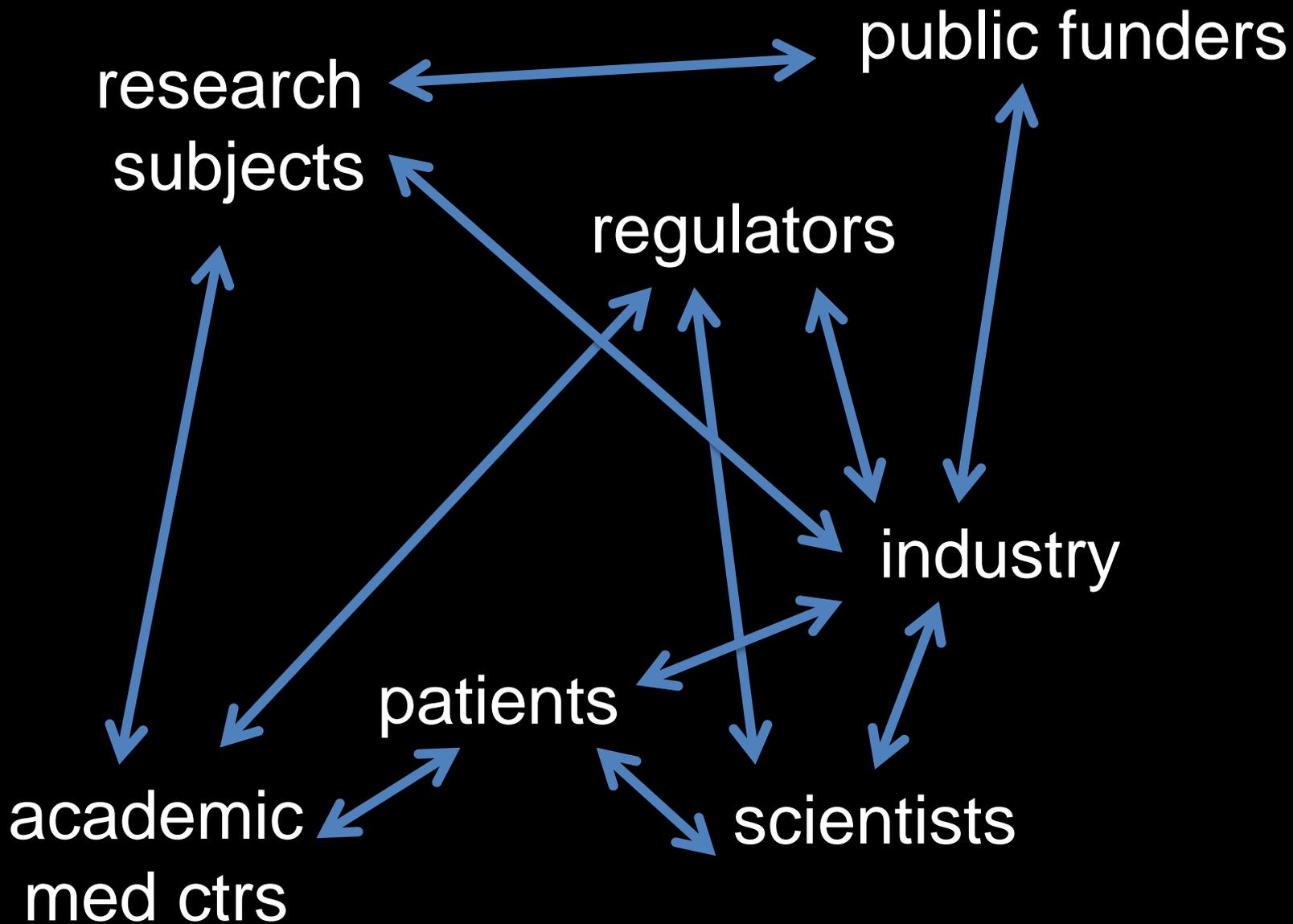
~~• minimal risk~~

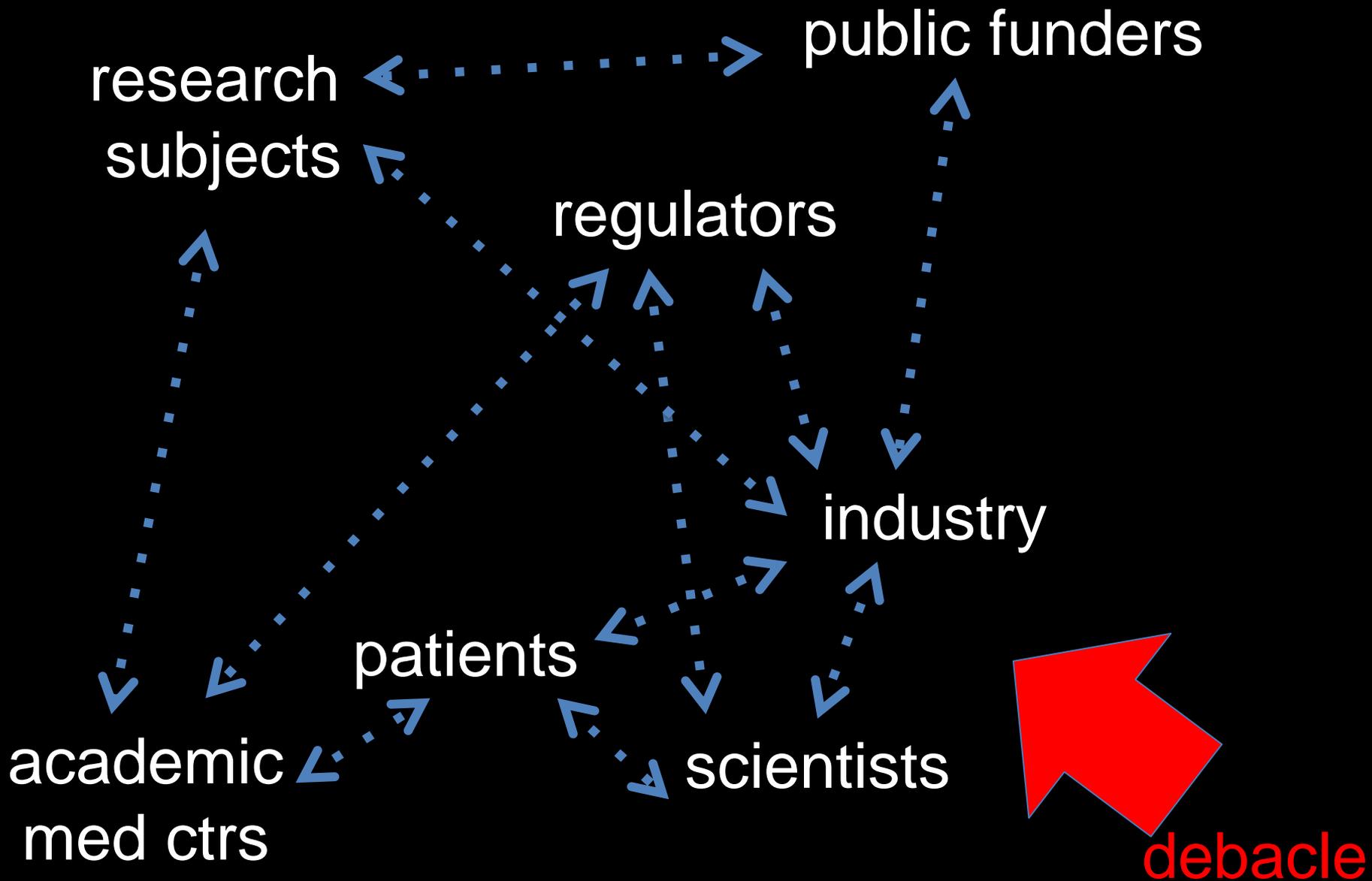
~~• minor increase > minimal~~

~~• therapeutic~~

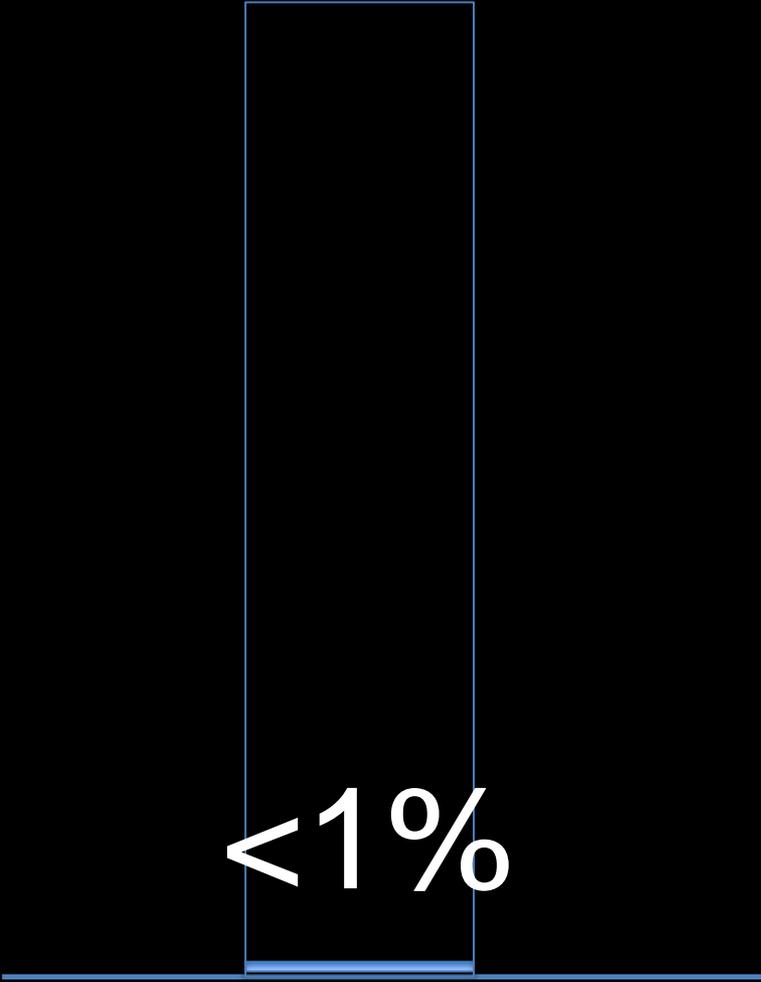


4: ethics of pre-license  
drug trials involves factors  
beyond human protection





**5: design early phase studies  
so that (-)'s are informative**



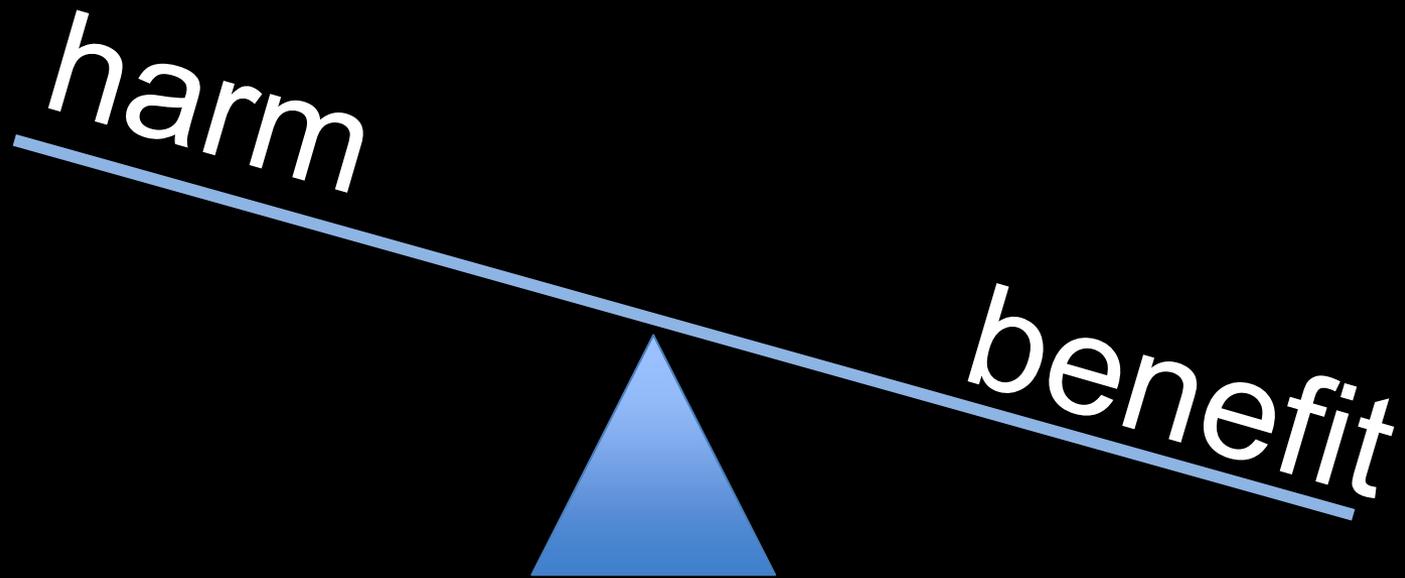
A bar chart with a black background. A single vertical bar is shown, outlined in white. The bar is mostly empty, with a very thin blue segment at the bottom. A horizontal blue line is drawn across the bottom of the chart area. The text "<1%" is written in white inside the bar, positioned above the blue segment.

<1%

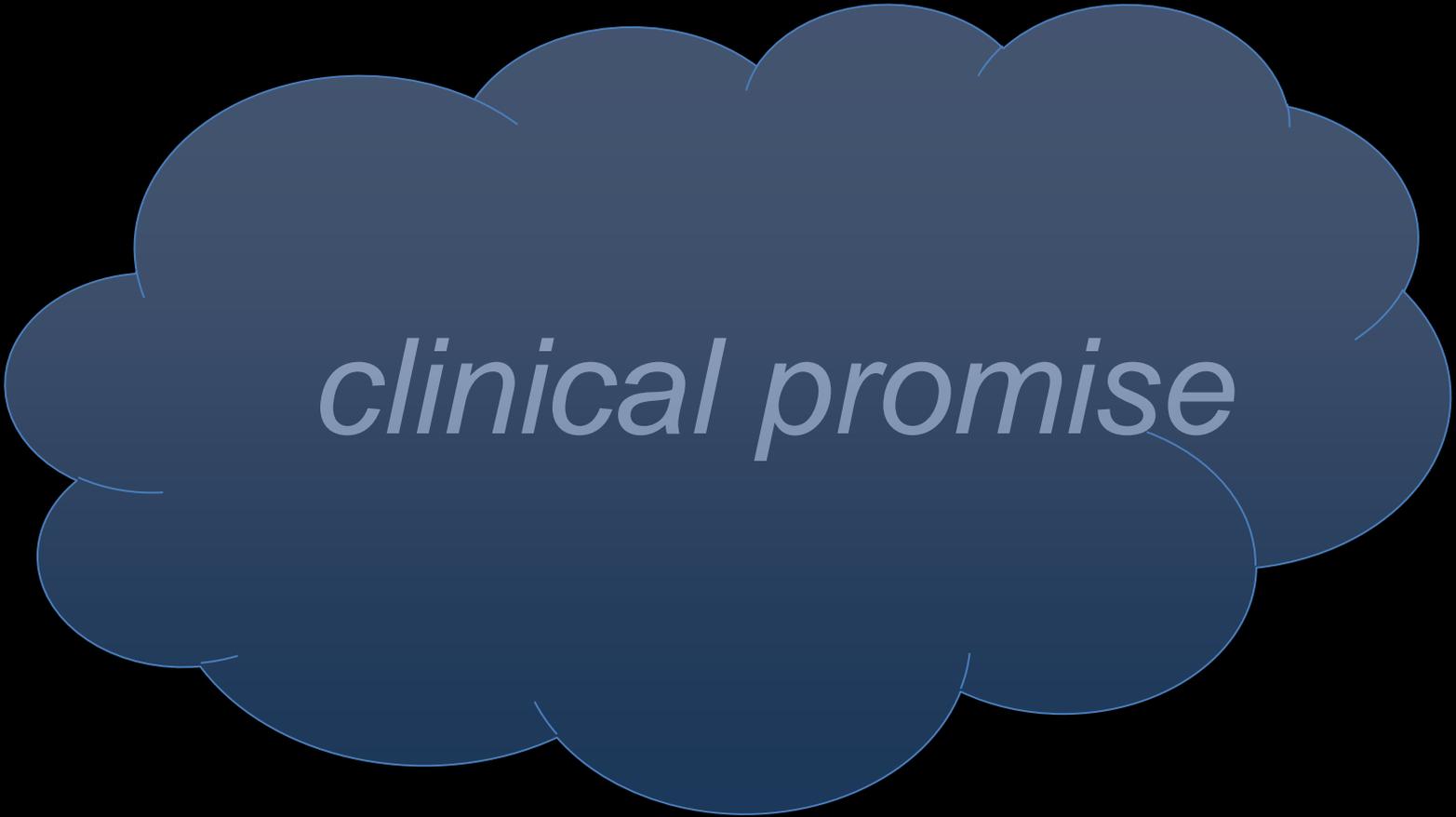


- rigorous, prespecified design
- correlative studies
- standardized protocols
- biobanking
- autopsy

6: among biggest ethical problems  
in neuro drug development:  
trial evidence inaccessible



benefit = value of knowledge



*clinical promise*

amyloid precursor protein

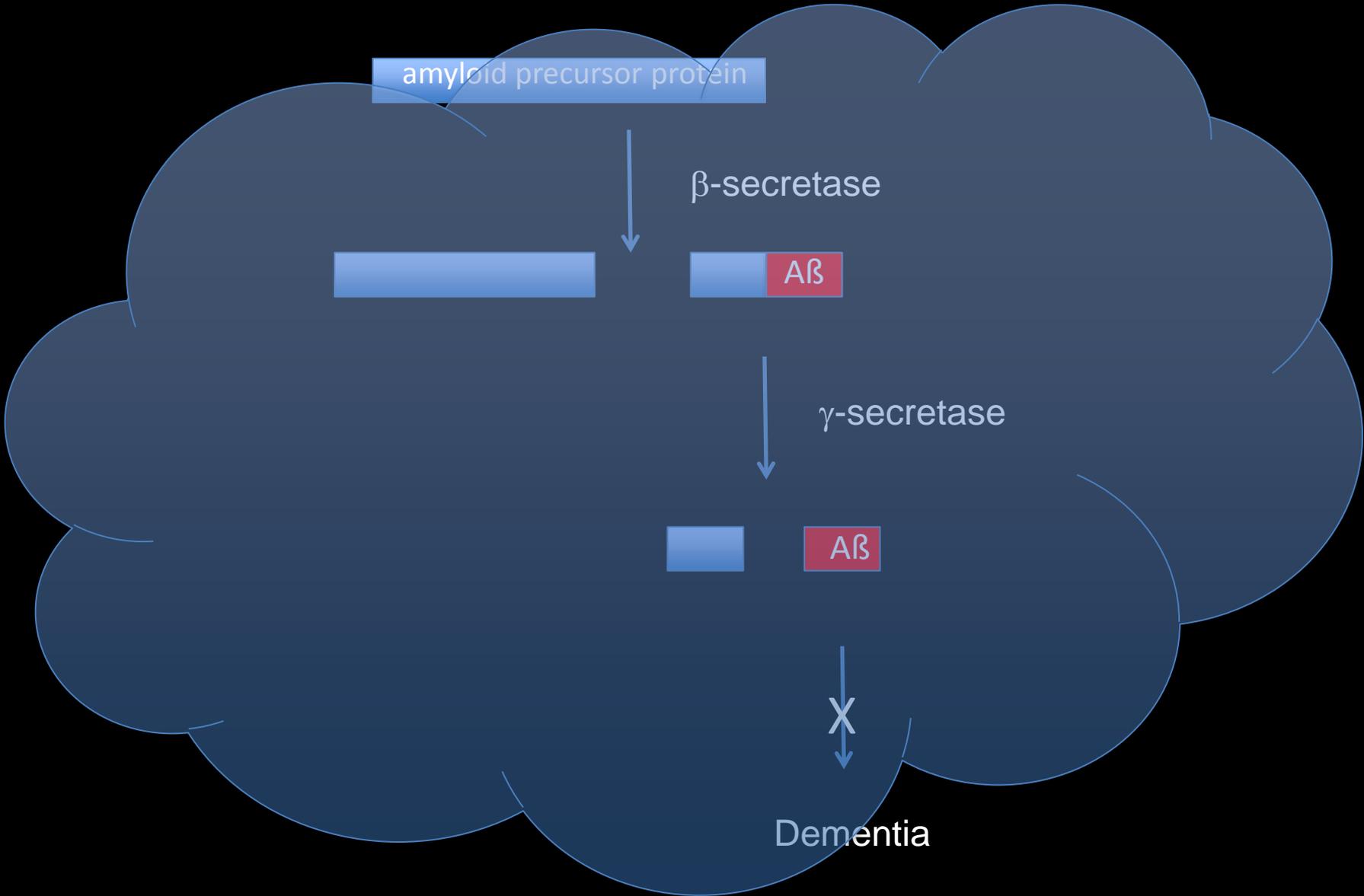
$\beta$ -secretase

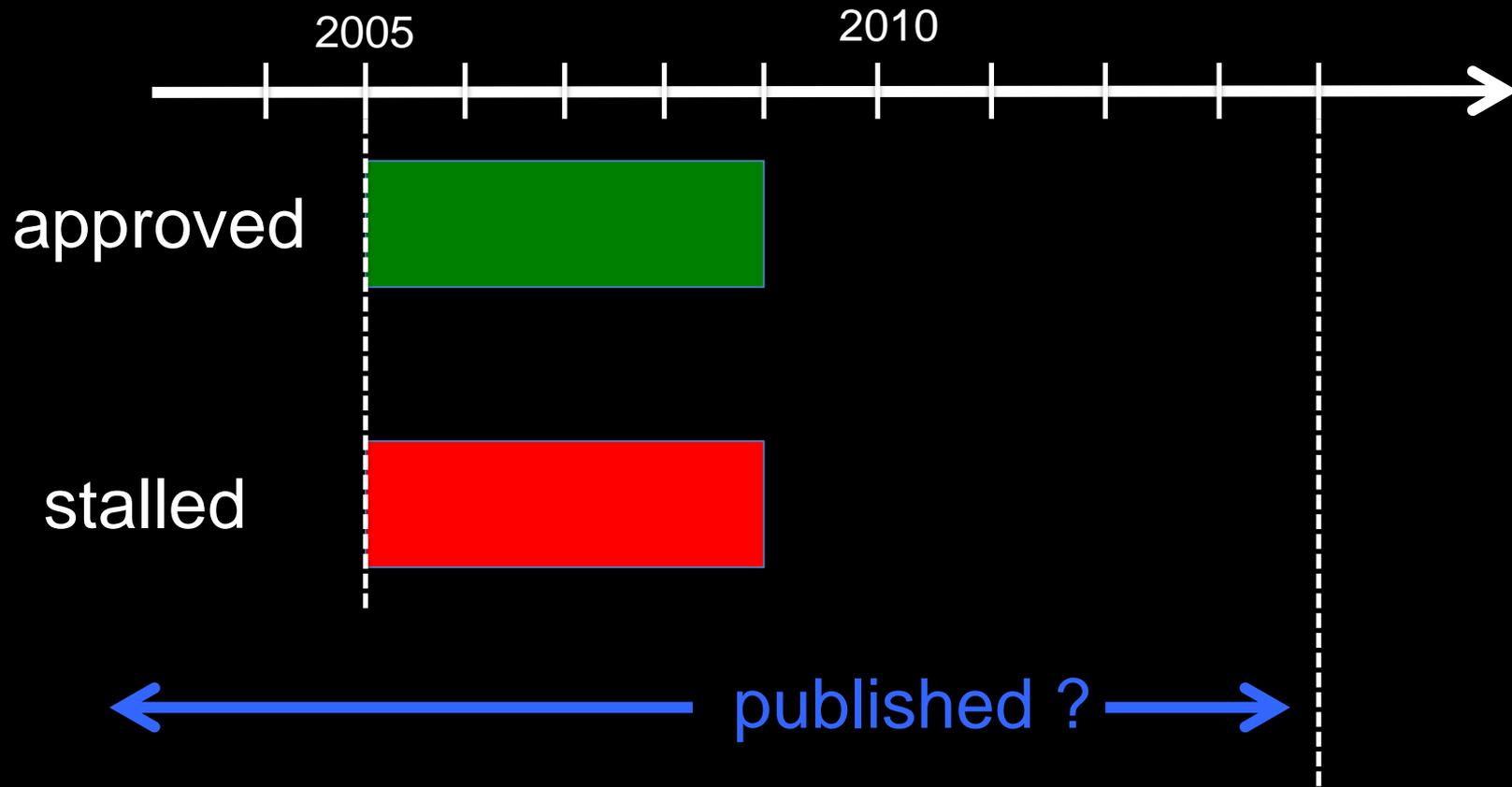
A $\beta$

$\gamma$ -secretase

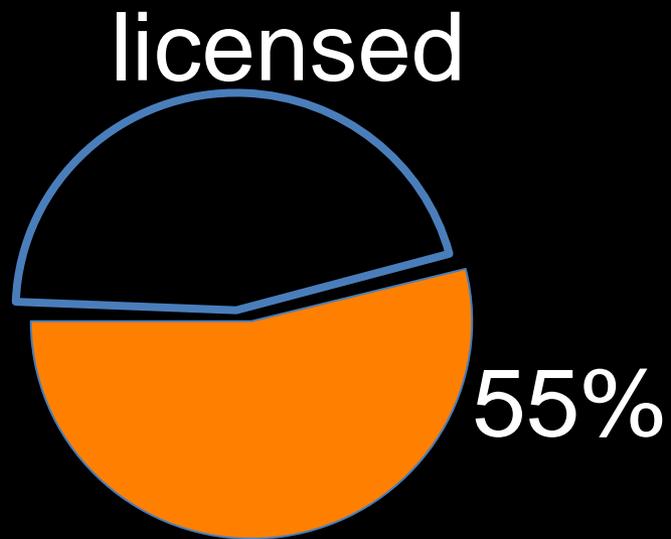
A $\beta$

~~X~~  
Dementia

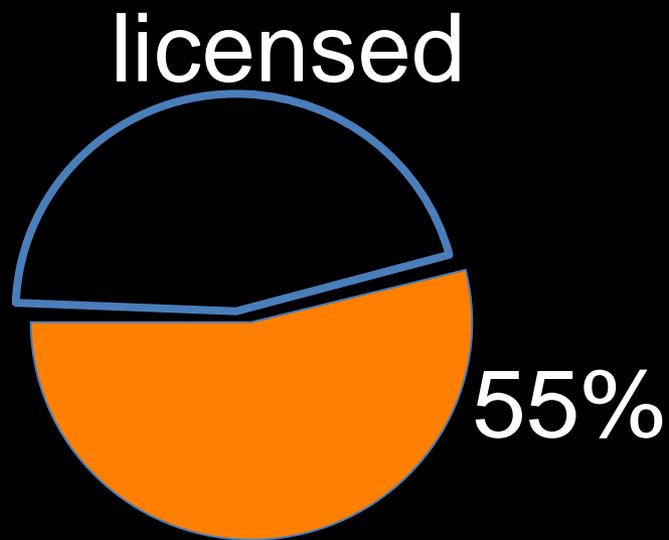




$p(\text{publication by year 5})$



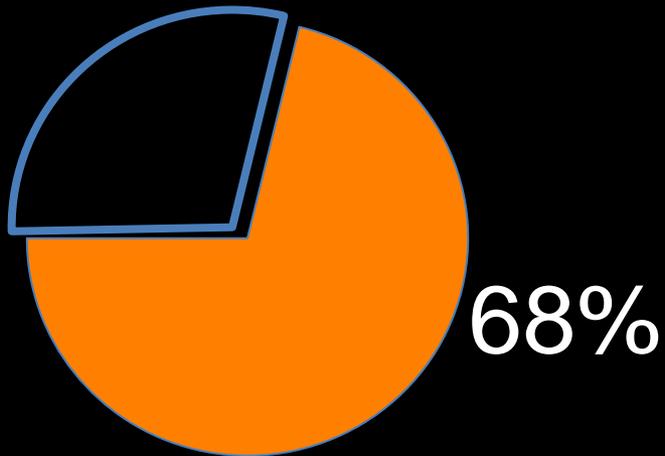
# p(publication by year 5)



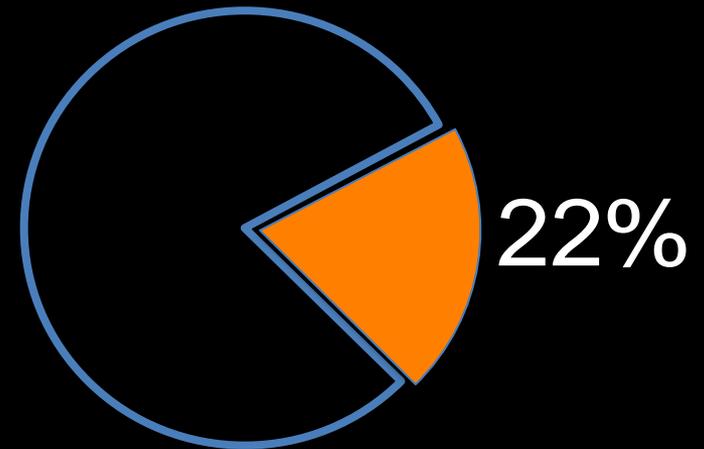
p(publication by year 5)

phase III

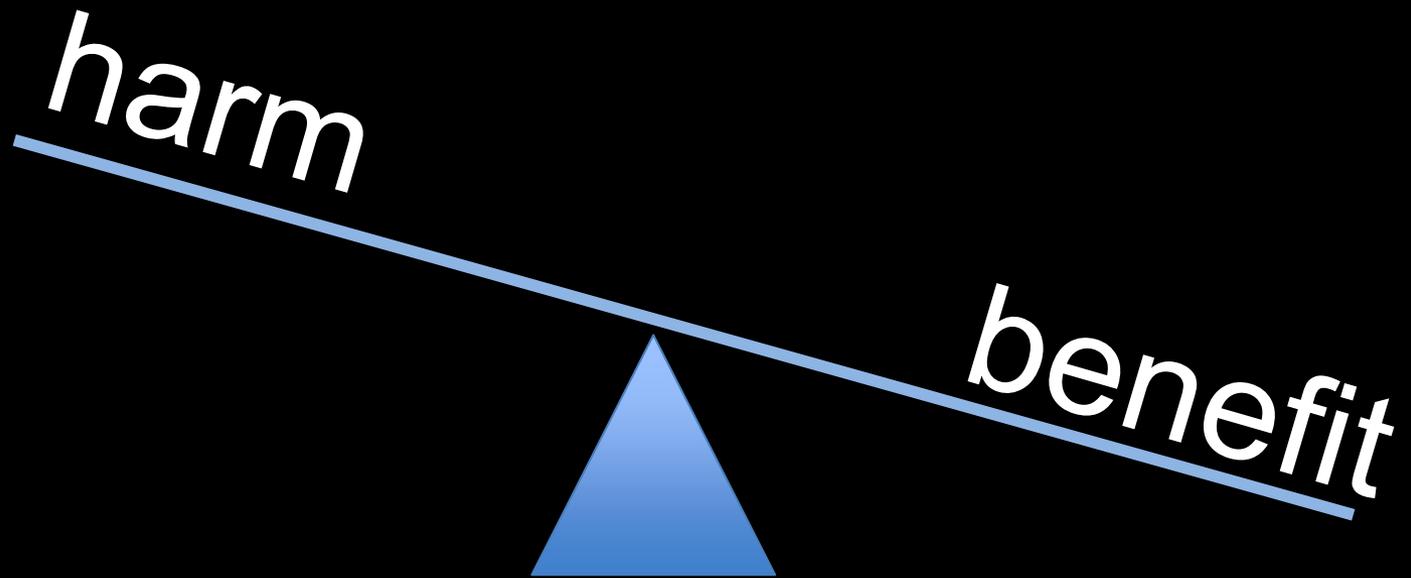
licensed



'stalled'







FDA

NIH

academic med ctrs  
investigators...

...and yes,  
industry



CIHR IRSC



**Alexander von Humboldt**  
Stiftung/Foundation