

What is the place of patients in First-in-Human (FiH) trials?

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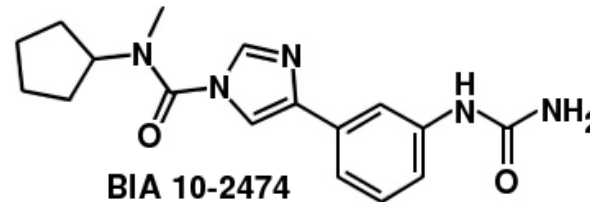
Place of patients in FiH* trials?

Incidents happen & shape the future

First-in-Human Clinical Trials — What We Can Learn from Tragic Failures

Sergio Bonini, M.D., and Guido Rasi, M.D.

On January 10, 2016, a healthy volunteer who had received 50 mg per day of a fatty acid amide hydrolase (FAAH) inhibitor for 5 days as part of a first-in-human phase 1 clinical trial was admitted to Rennes University Hospital with neurologic and gait disturbances. After a dramatic worsening of neurologic symptoms, the participant died on January 17.



TO THE EDITOR: Kerbrat et al. and Bonini and Rasi describe a phase 1 study that underwent review by an institutional review board. Nevertheless, I question whether it is ethical to enroll healthy persons in phase 1 (toxicity) trials.

According to the principle described in the Belmont Report,¹ beneficence implies a reasonable risk-to-benefit ratio. For a healthy volunteer enrolling in a toxicity trial, there is clearly risk but no medical benefit. Monetary compensation or appeals to altruism in the name of humankind are only avenues for ethical abuse. The only cohort that can be considered to derive at least a modicum of medical benefit from volunteering

in a phase 1 trial consists of patients who have the condition for which the drug is being developed as a treatment. They should be the only persons who are asked to volunteer for a phase 1 trial.

Irwin Nash, M.D.

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N Engl J Med 2017; 376: 393

N Engl J Med 2016; 375: 1717-1725

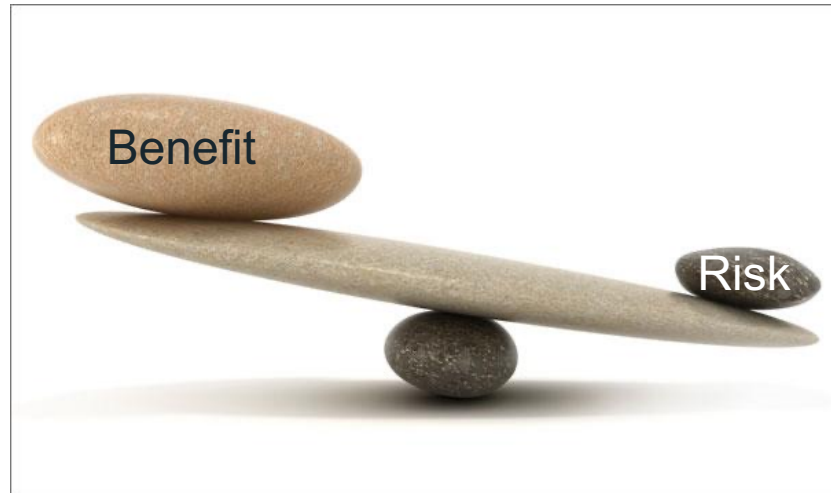
* FiH: initial testing of IMP in human

Place of patients in FiH trials?

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Place of patients in FiH trials?

A reality check (1)

Navigating First-in-Human and Early-Phase Patient Studies: Study Designs, Risk Mitigation, and Population Selection Challenges

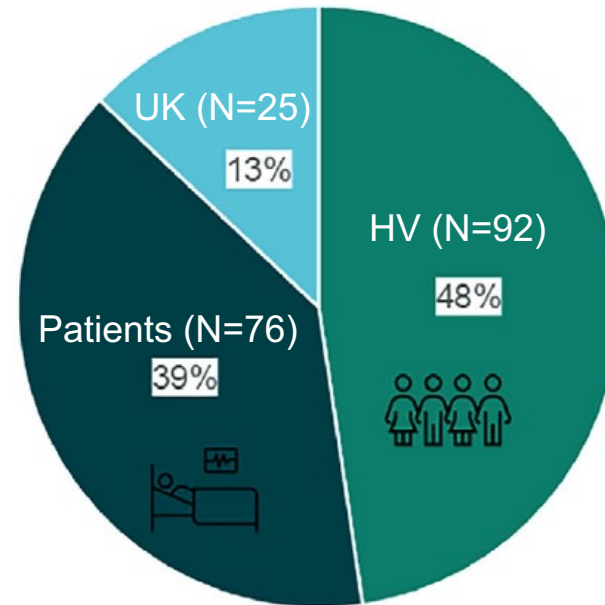
J. Courville et al. *J Clin Pharmacol* 2025

- Review period: 2020 – 2023
- 193 FDA approved compounds*
 - small molecules
 - biologicals
- FiH populations in SAD / MAD trials

Study population for FIH/initial SAD/MAD based on FDA approvals (Jan 2020-Dec 2023)

Non-oncology trials:

- Genetic and rare diseases
- Autoimmune diseases



■ FIH in Healthy population
■ FIH not in Healthy population
■ unknown

* Excluding cell therapies, blood products and vaccines

Place of patients in FiH trials?

A reality check (2)

Navigating First-in-Human and Early-Phase Patient Studies: Study Designs, Risk Mitigation, and Population Selection Challenges

J. Courville et al. *J Clin Pharmacol* 2025

- Review period: 2020 – 2023
- 193 FDA approved compounds*
 - small molecules
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- FiH populations in SAD / MAD trials

Healthy subjects

Patients

Shift in FiH / early clinical trial populations driven by:

- Treatment options:
 - small molecules, biologicals, ATMPs
- Safety: risk – benefit assessment
 - nature of the IMP, including MoA
 - procedures and interventions
 - improving prediction and simulation tools
- Patient relevance:
 - rare diseases
 - genetic disorders

* Excluding cell therapies, blood products and vaccines

Place of patients in FiH trials?

Considerations: pros & cons (1)

<i>Healthy subjects</i>			<i>Patients</i>		
Considerations		Healthy volunteers	Patients		
Objectives		safety & tolerability	efficacy		

Place of patients in FiH trials?

Considerations: pros & cons (2)

<i>Healthy subjects</i>		<i>Patients</i>
Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter

Place of patients in FiH trials?

Considerations: pros & cons (3)

<i>Healthy subjects</i>		<i>Patients</i>
Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter
Recruitment & enrollment	fast	slow

Place of patients in FiH trials?

Considerations: pros & cons (4)



Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter
Recruitment & enrollment	fast	slow
Data collection	intense	demanding
Data quality	robust, high-quality	variable, (AE) interpretation

Place of patients in FiH trials?

Considerations: pros & cons (5)



Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter
Recruitment & enrollment	fast	slow
Data collection	intense	demanding
Data quality	robust, high-quality	variable, (AE) interpretation
Dose selection*	MRSD / MABEL / placebo	(low) ATD / subtherapeutic

* MRSD: Maximal Recommended Starting Dose; MABEL: Minimal Anticipated Biological Effect Level; ATD: Anticipated Therapeutic Dose

Place of patients in FiH trials?

Considerations: pros & cons (6)



Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter
Recruitment & enrollment	fast	slow
Data collection	intense	demanding
Data quality	robust, high-quality	variable, (AE) interpretation
Dose selection	MRSD / MABEL / placebo	(low) ATD / subtherapeutic
Pharmacokinetics	clean	DDI, co-morbidity
Pharmacodynamics	biomarker	target expression

Place of patients in FiH trials?

Considerations: pros & cons (7)



Considerations	Healthy volunteers	Patients
Objectives	safety & tolerability	efficacy
Logistic & operational	easy / single center	complicated / multicenter
Recruitment & enrollment	fast	slow
Data collection	intense	demanding
Data quality	robust, high-quality	variable, (AE) interpretation
Dose selection	MRSD / MABEL / placebo	(low) ATD / subtherapeutic
Pharmacokinetics	clean	DDI, co-morbidity
Pharmacodynamics	biomarker	target expression
Ethical	no (medical) benefit	non-therapeutic / placebo

Place of patients in FiH trials?

Considerations: pros & cons (8)

<i>Healthy subjects</i>		<i>Patients</i>	
Considerations	Healthy subjects	Patients	
Objectives	safety		efficacy
Logistic & operational	easy		complicated / multicenter
Recruitment & enrollment	fast		slow
Data collection	simple		demanding
Data quality		Part 1 / SAD: HV	variable, (AE) interpretation
Dose selection		Part 2 / MAD: patients	(low) ATD / subtherapeutic
Pharmacokinetics		2 step approach:	renal, co-morbidity
Pharmacodynamics		“HYBRID” study design	target expression
Ethical			therapeutic / placebo

Place of patients in FiH trials?

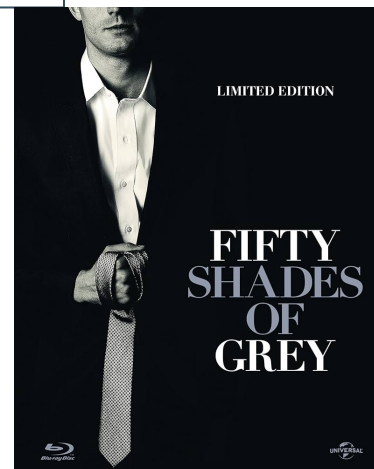
Target population: healthy subjects versus patients

Healthy subjects

Patients

The **target population** is not a matter of “black & white”

- Healthy subjects:
 - prophylactic vaccines
 - procedural sedation



Place of patients in FiH trials?

Target population: healthy subjects versus patients

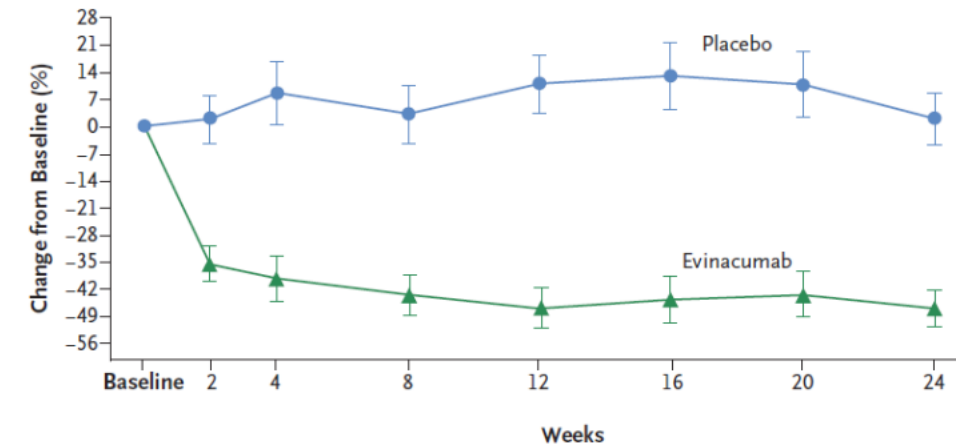
Healthy subjects

Patients

The **target population** is not a matter of “black & white”

- Healthy subjects:
 - prophylactic vaccines
 - procedural sedation
- Healthy “patients”:
 - healthy obese subjects
 - healthy subjects with hypercholesterolemia

A Percent Change in LDL Levels



No. at Risk

Placebo	22	19	20	21	20	20	20	21
Evinacumab	43	38	43	42	42	40	43	43

NEJM 2020; 383: 711

Place of patients in FiH trials?

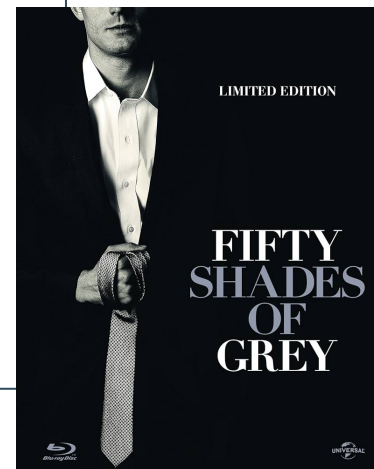
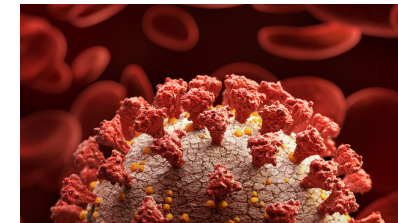
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- “Artificial patients” by provocation of disease:
 - Controlled Human Infection Model (CHIM) trials
 - provocation of migraine headache



Place of patients in FiH trials?

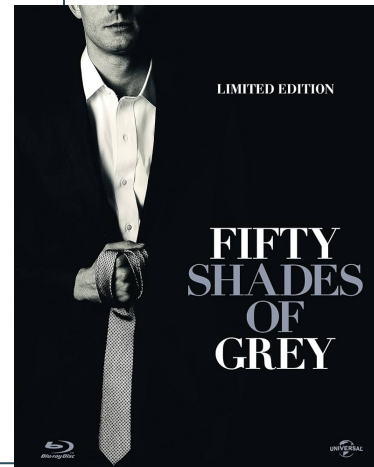
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- “Artificial patients” by provocation of disease:
 - Controlled Human Infection Model (CHIM) trials
 - provocation of migraine headache
- “Real” patients...





**THANK
YOU**

Any Questions?

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