Ethical Dimensions of FIH Gene Transfer Trials

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STREAM

Studies of Translation, Ethics and Medicine

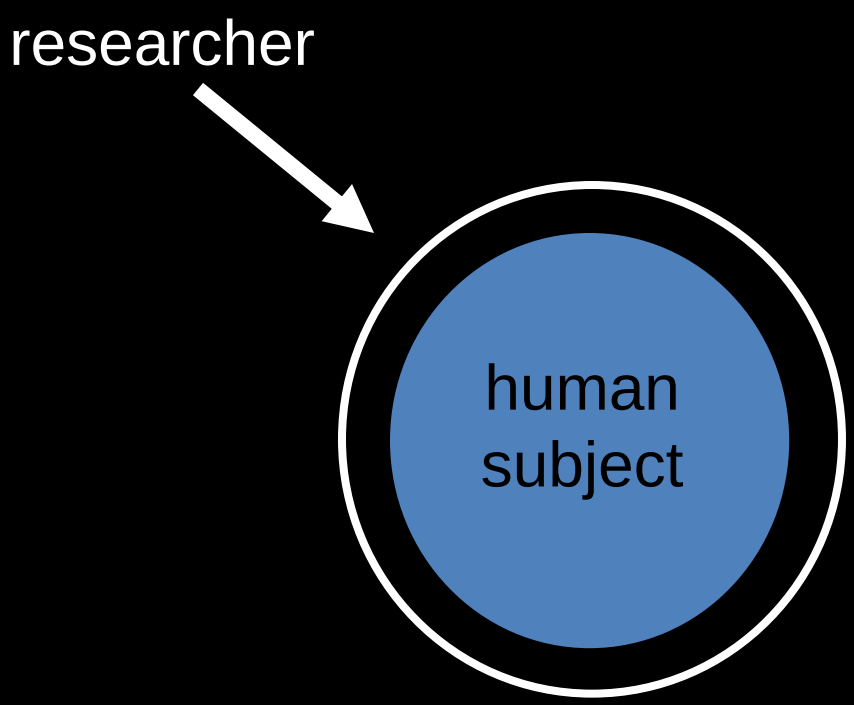
CoI disclosure:

Ultragenyx: DSMB member / <$5K/yr.

1A. fundamentals / ethics

2

Photocredit: NIH, Wikimedia


researcher
human
subject

3 parts

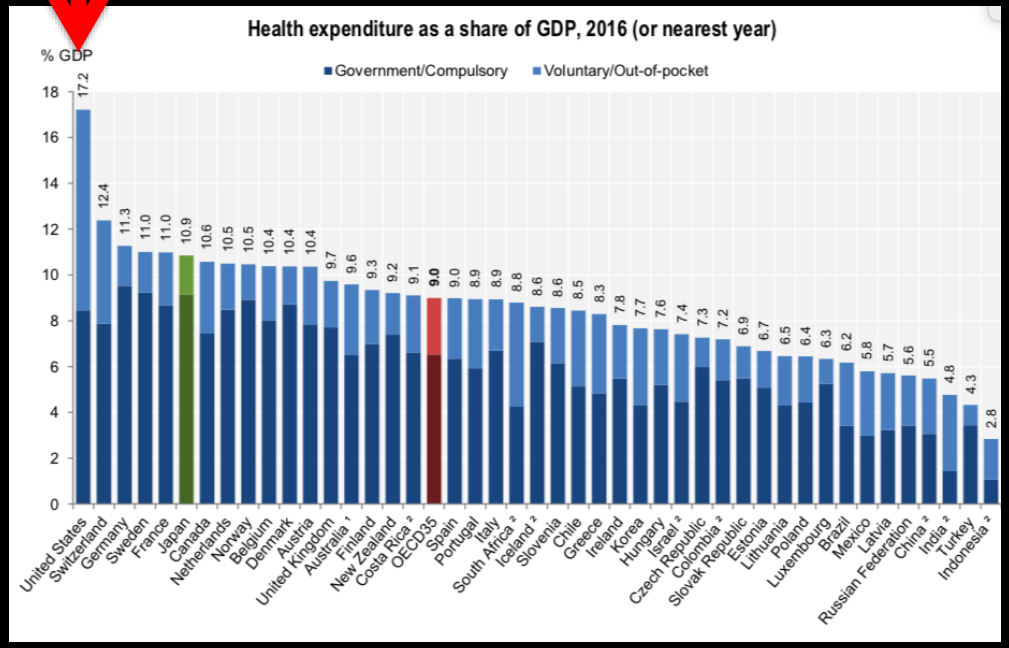
1)

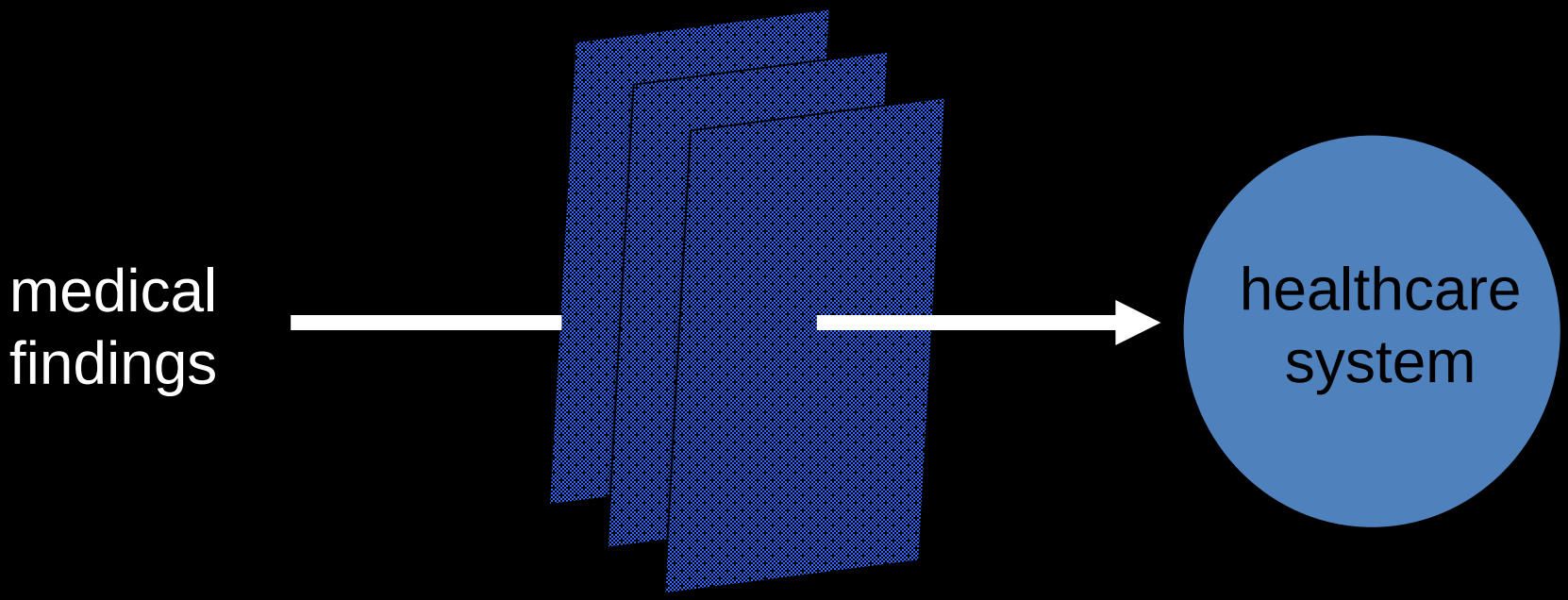
Photocredit: Urcommunicacion, Wikimedia

2)

Photocredit: NIH, Wikimedia

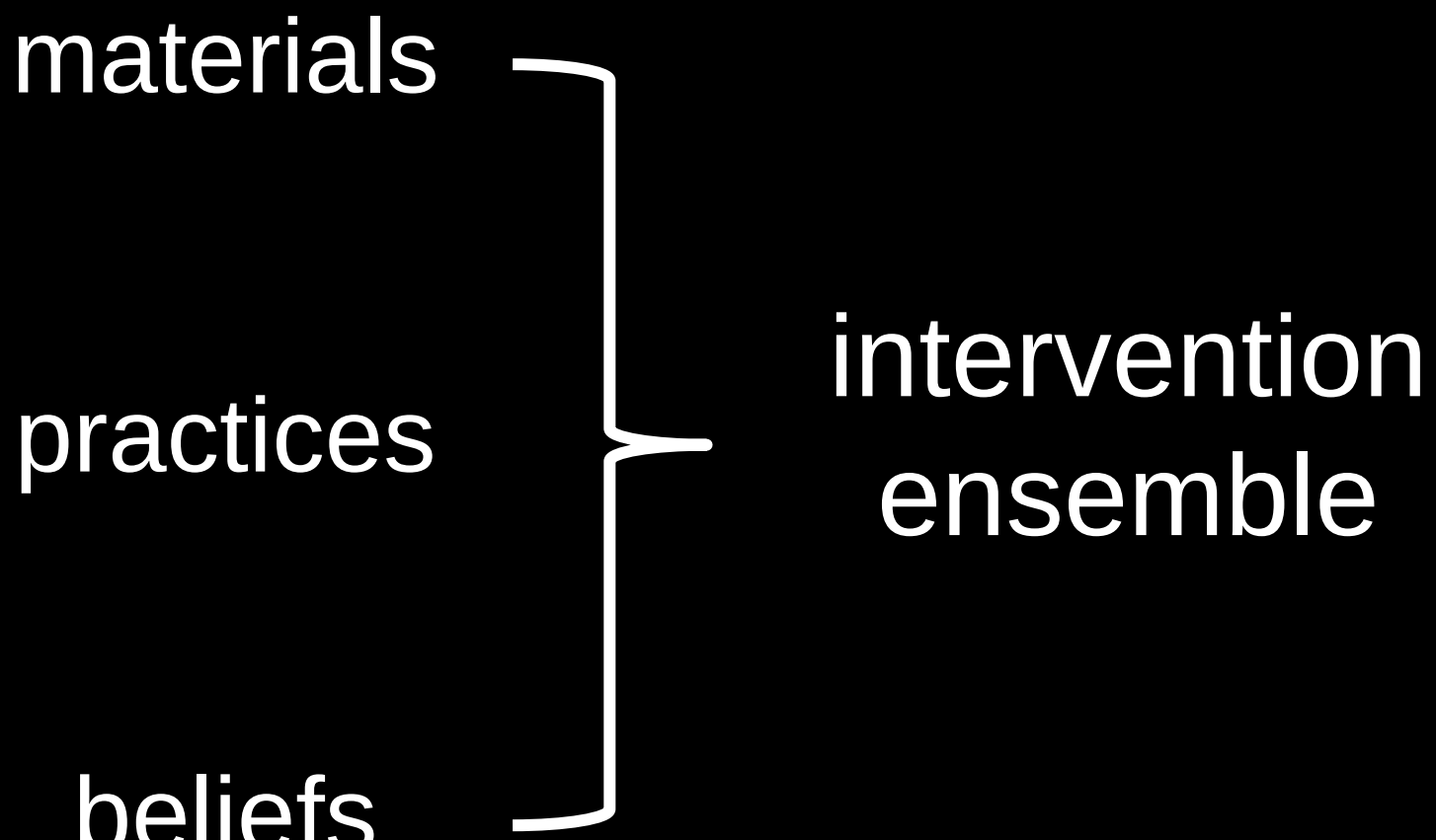
3)

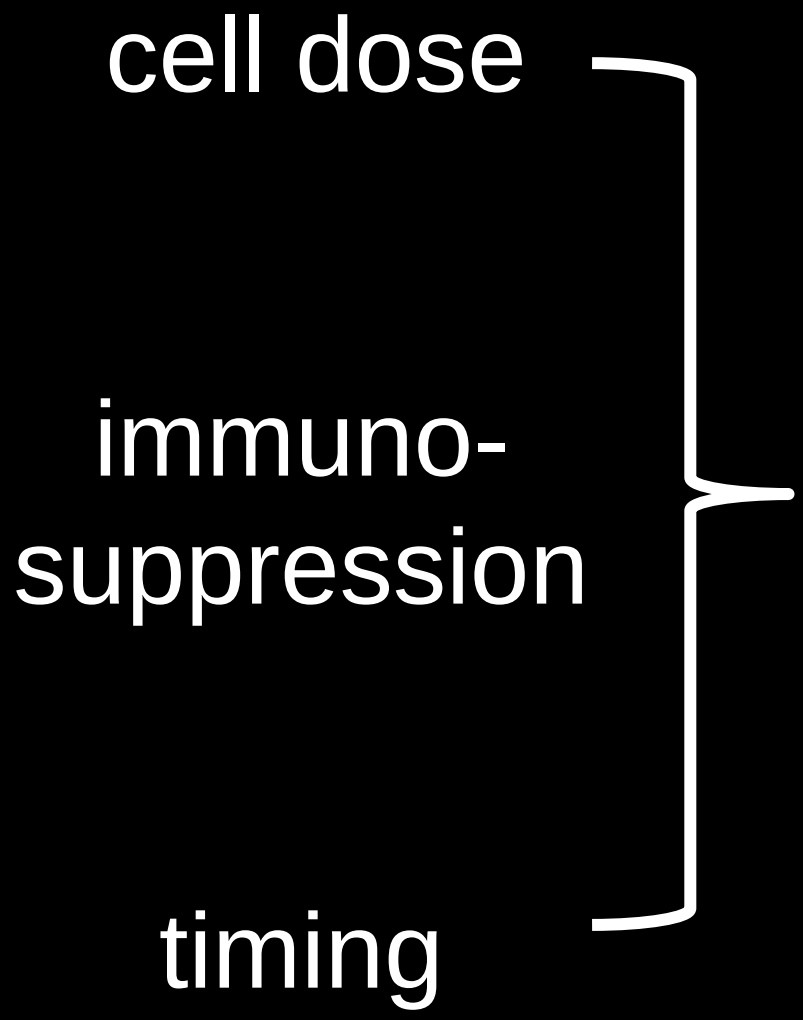

Health expenditure as a share of GDP, 2016 (or nearest year)
% GDP
Government/Compulsory
Voluntary/Out-of-pocket
0
2
4
6
8
10
12
14
16
18
17.2
12.4
11.3
11.0
11.0
10.9
10.6
10.5
10.5
10.4
10.4
10.4
9.7
9.6
9.3
9.2
9.1
9.0
9.0
8.9
8.9
8.8
8.6
8.6
8.5
8.3
7.8
7.7
7.6
7.4
7.3
7.2
6.9
6.7
6.5
6.4
6.3
6.2
5.8
5.7
5.6
5.5
4.8
4.3
2.8
United States
Switzerland
Germany
Sweden
France
Japan
Canada
Netherlands
Norway
Belgium
Denmark
Austria
United Kingdom
Australia 1
Finland
New Zealand
Costa Rica 2
OECD35
Spain
Portugal
Italy
South Africa 2
Iceland 2
Slovenia
Chile
Greece
Ireland
Korea
Hungary
Israel 2
Czech Republic
Colombia 2
Slovak Republic
Estonia
Lithuania
Poland
Luxembourg
Brazil
Mexico
Latvia
Russian Federation
China 2
India 2
Turkey
Indonesia 2

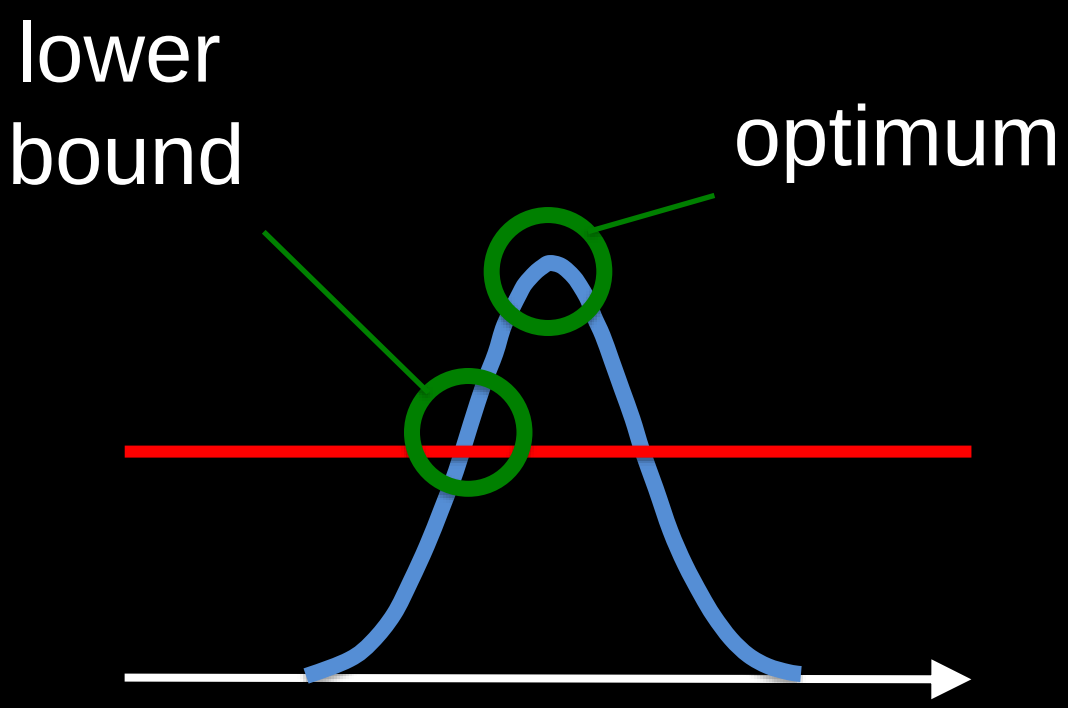

medical
findings
healthcare
system

1B. fundamentals / science

2


materials
practices
beliefs
intervention
ensemble


cell dose
immuno-
suppression
timing
cell therapy
for ALS


lower
bound
optimum

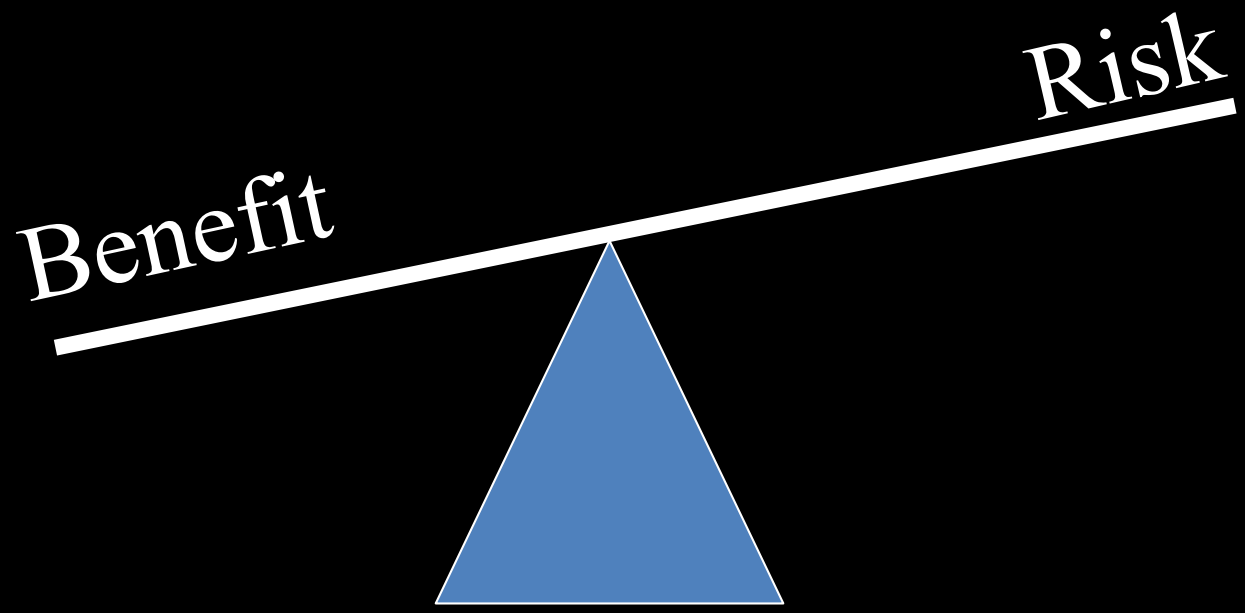
dose
imm. suppr.
timing
etc.

intervention ensemble

dose
imm. suppr.
timing
etc.

intervention ensemble

2. when to begin


Benefit
Risk

FDA Guidance on INDs for Phase 1

To the extent that such studies may be important to address safety issues, or to assist in evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.

FDA Guidance on INDs for GT /CT

A. Preclinical Program Objectives

The preclinical studies that are conducted are an important element of the overall development pathway for an investigational product. The overall objectives for a sufficient preclinical program for a CGT product include, as applicable:

1. Establishment of biological plausibility.

2. Identification of biologically active dose levels.

of the proposed clinical trial. Features of study design, such as the inclusion of appropriate concurrent controls, randomization, or blinding methods, may increase the strength of the resulting study data, thus should be considered.

e.g. 2013

Stem Cell Reports
Article
OPEN ACCESS

Preclinical Efficacy Failure of Human CNS-Derived Stem Cells for Use in the Pathway Study of Cervical Spinal Cord Injury

Aileen J. Anderson,[1,2,3,4,*] Katja M. Piltti,[1,3] Mitra J. Hooshmand,[1,3] Rebecca A. Nishi,[1,3] and Brian J. Cummings[1,2,3,4]

$$\frac{\text{p(harm to subject)}}{\text{p(benefit to subject) + p(advance science)}}$$

patient

sponsor /
investigator

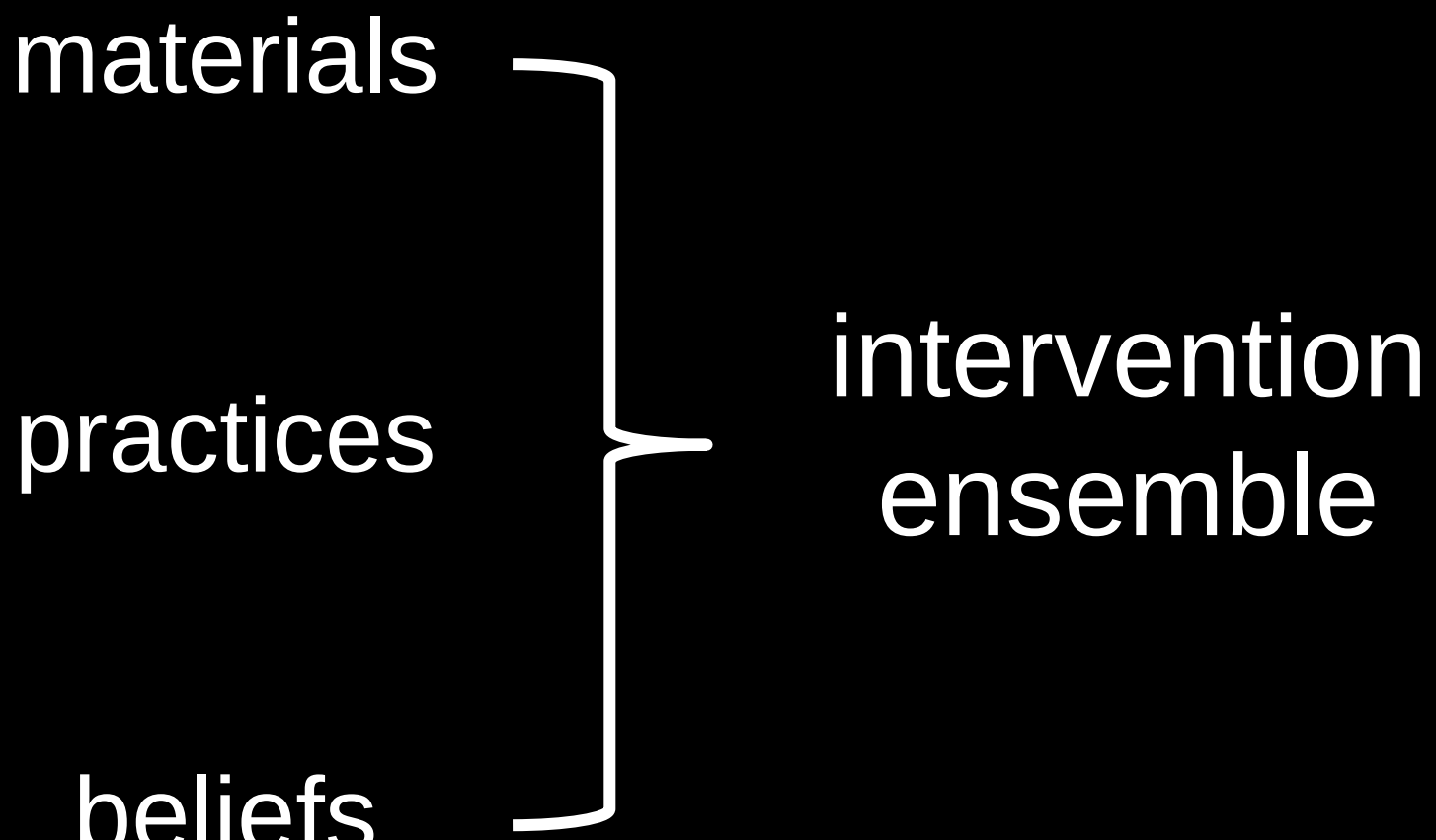
IRB

future pts

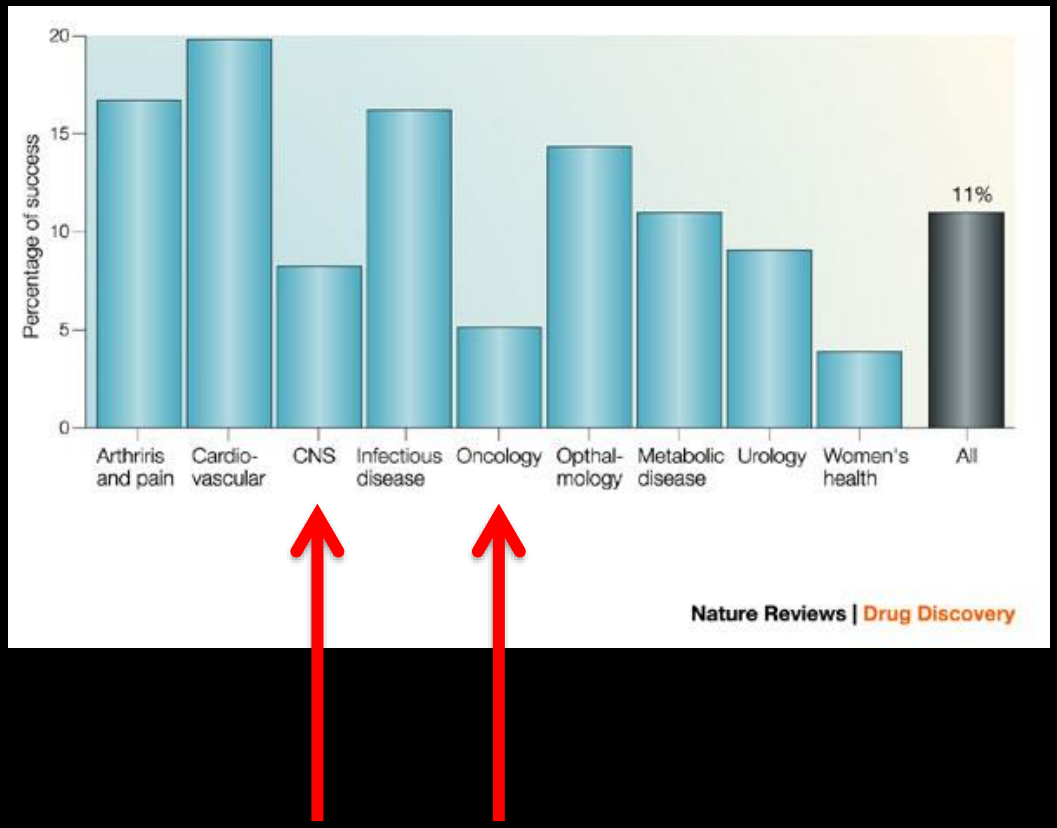
3. is it ‘therapy’ ?

2)

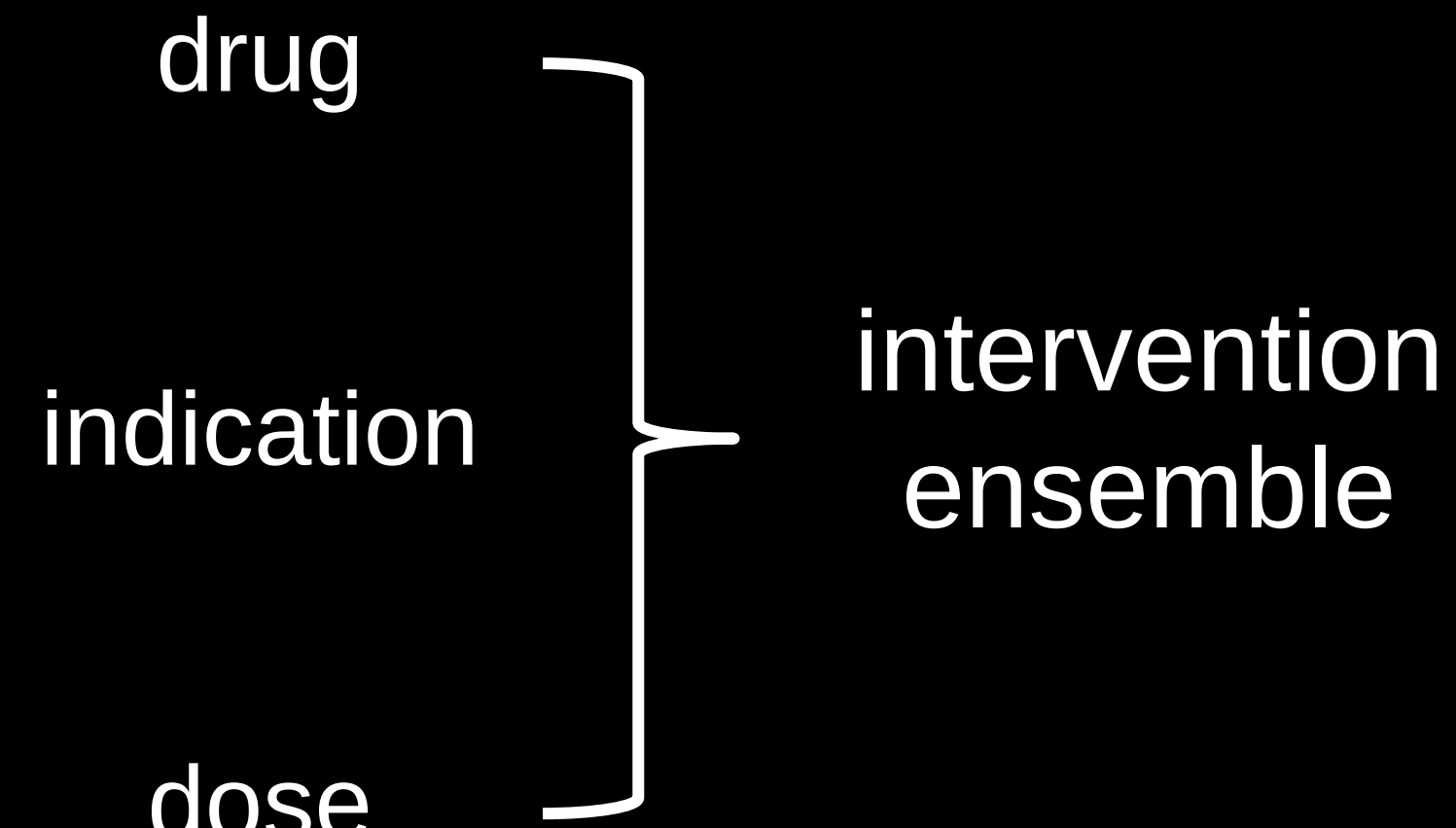
a) principle


materials
practices
beliefs
intervention
ensemble

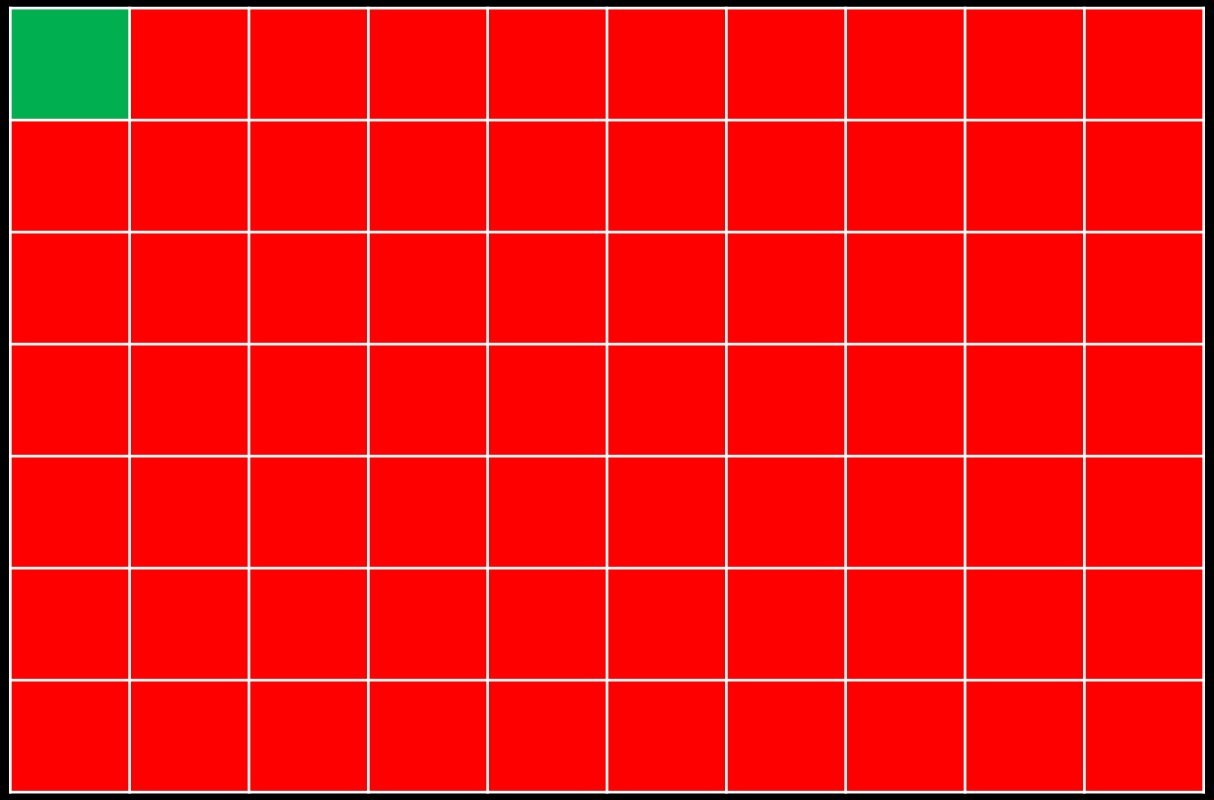
b) evidence



Source: Kola I, Landis J, NRRD 2004; 3: 711


drug
indication
dose
intervention ensemble

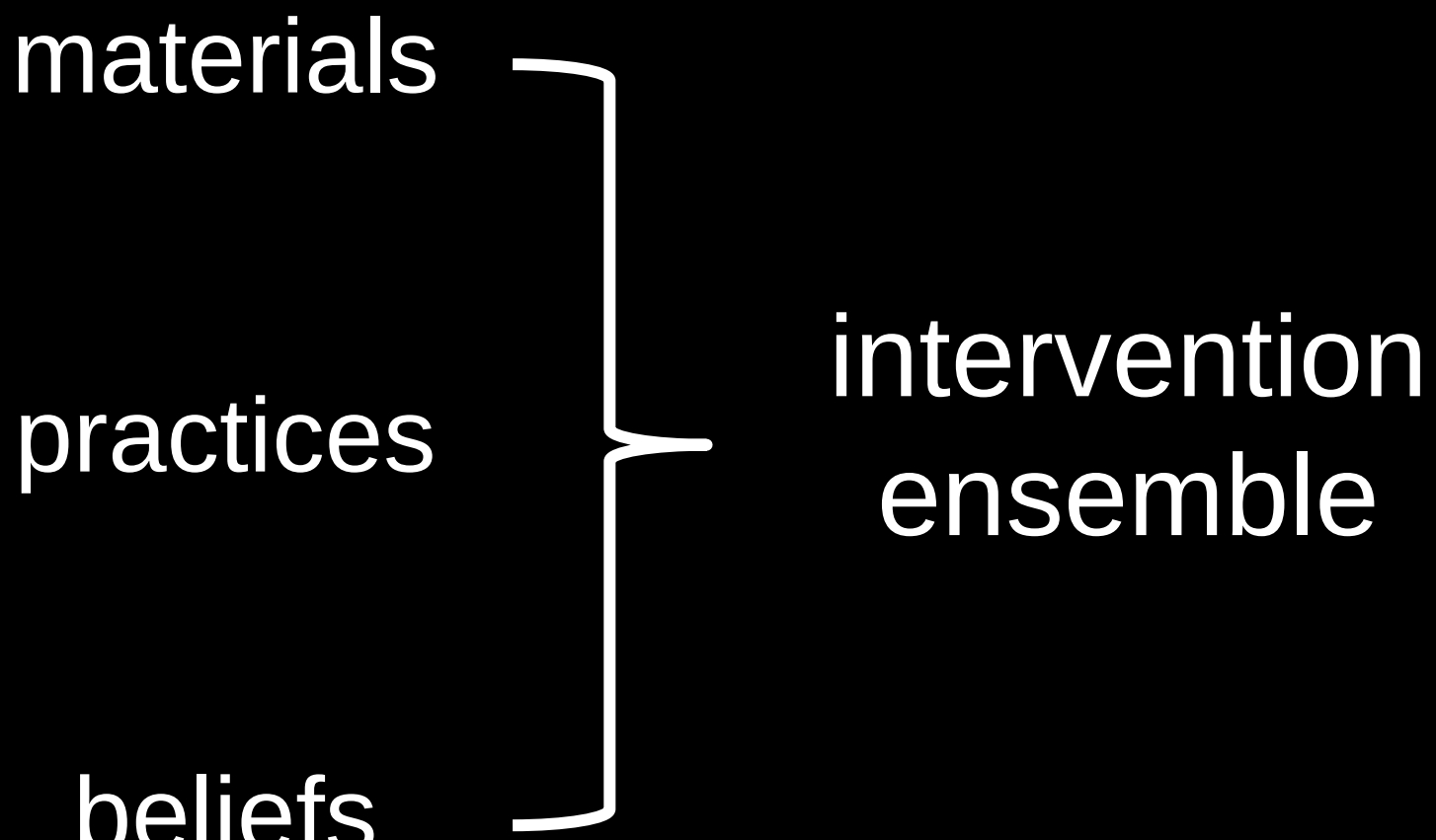
Phase 1: NNT = 70



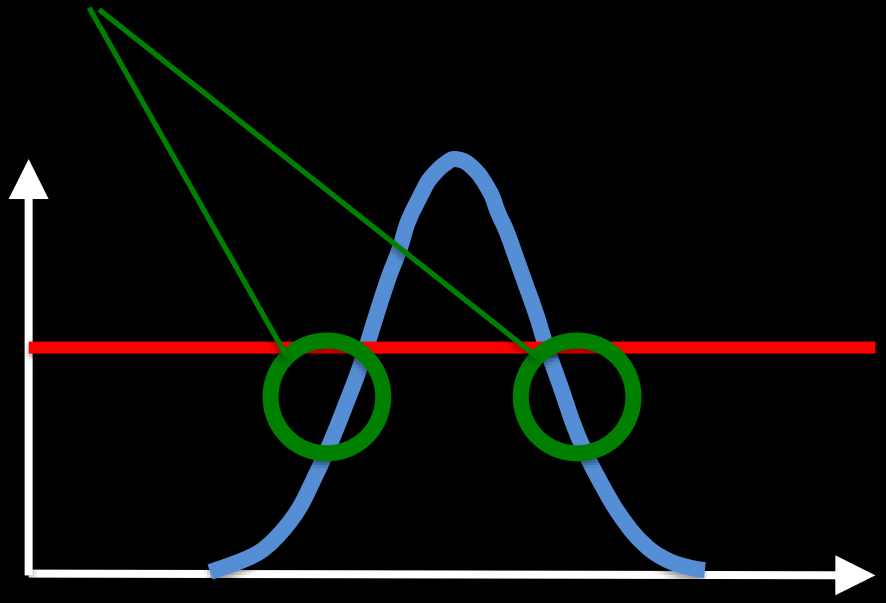
Zhang et al, submitted

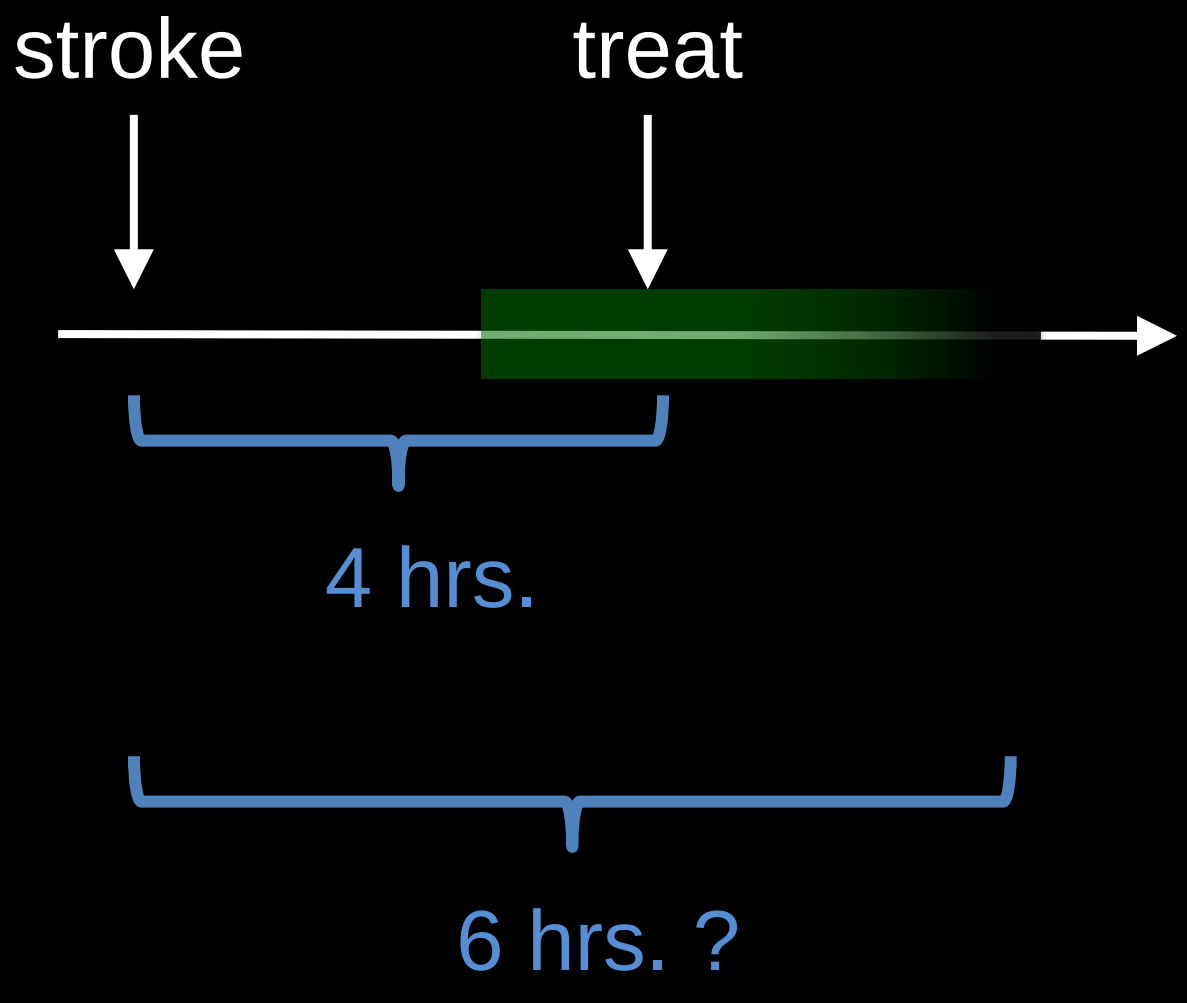
usually non-therapeutic

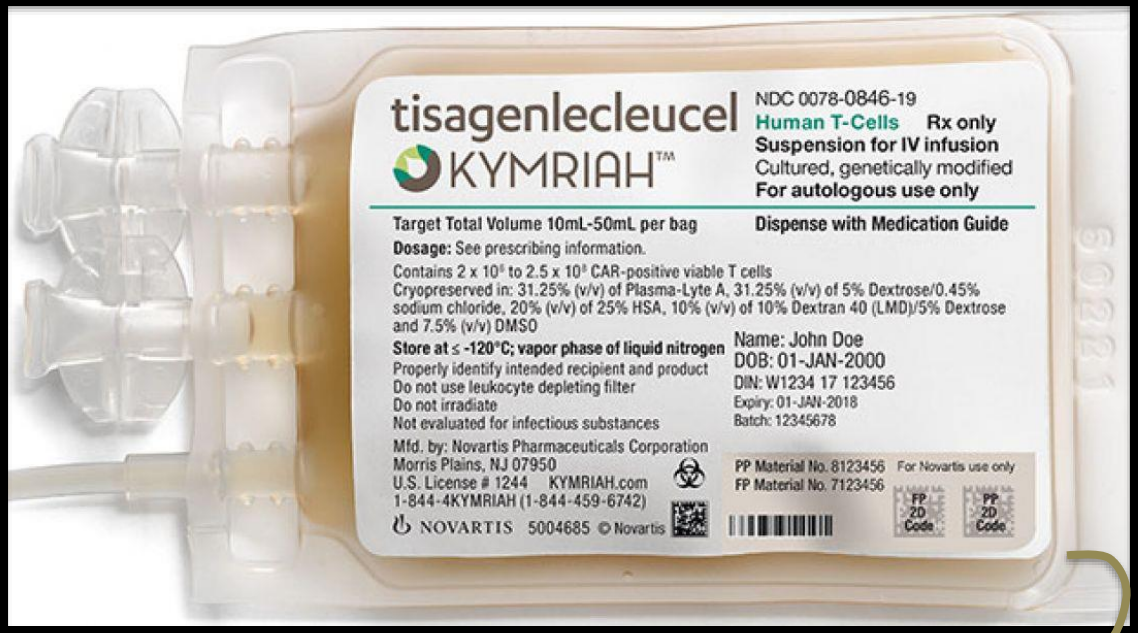
4. how to design ?


materials
practices
beliefs
intervention
ensemble

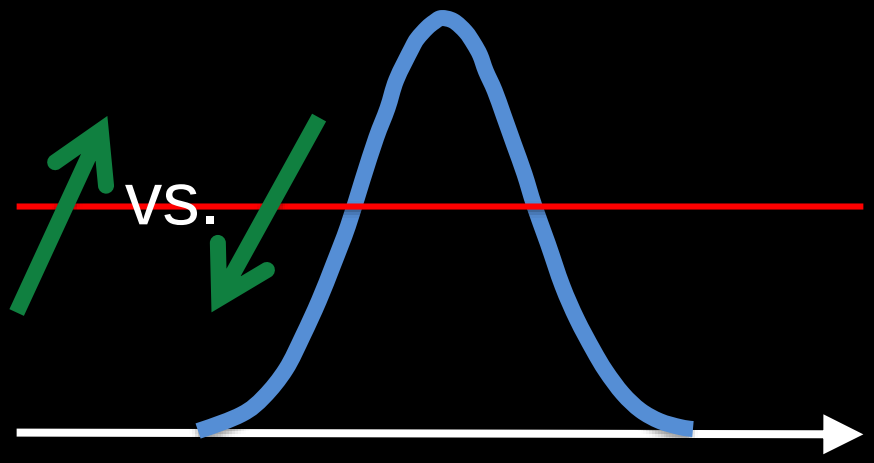
‘edges = 33%’



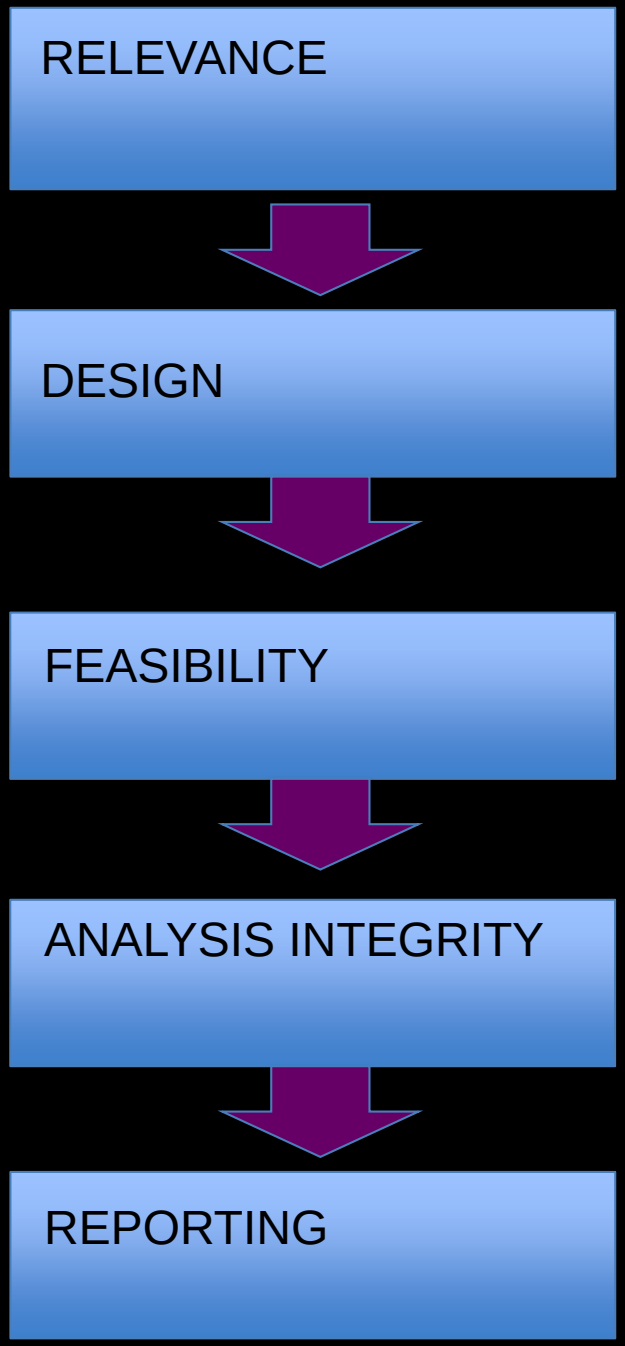

stroke
treat
4 hrs.
6 hrs. ?



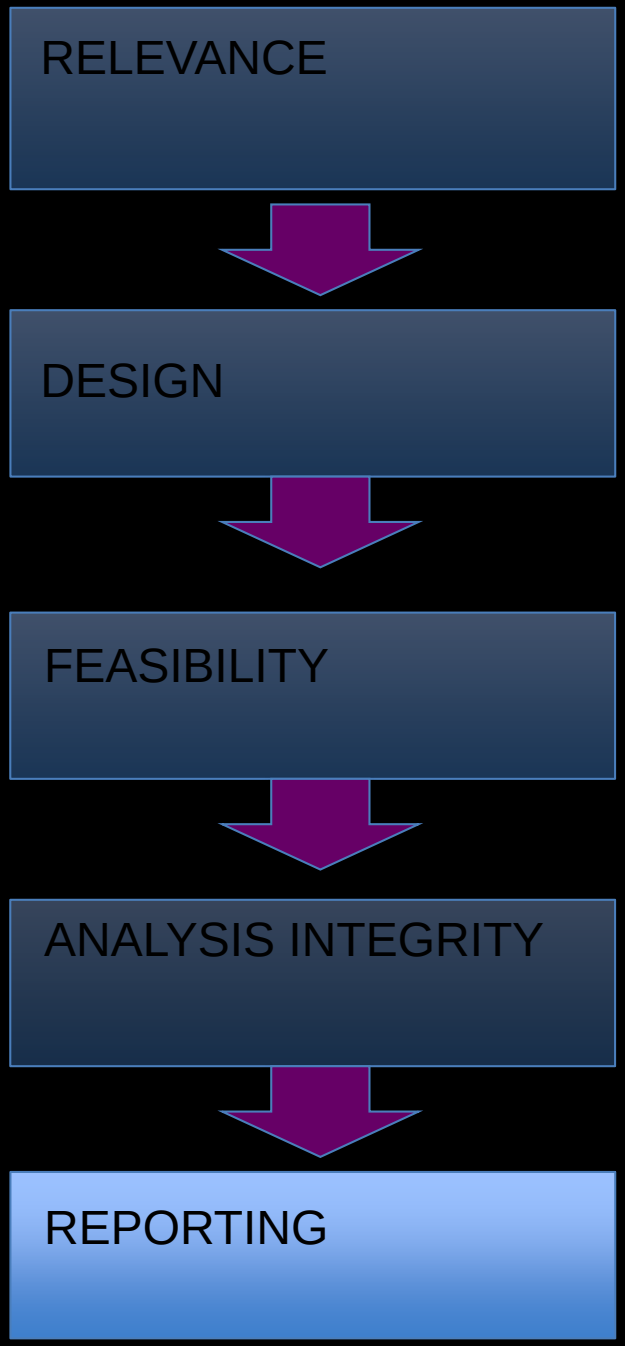
$ 475,000
ancillary Rx not included


vs.

5. informativeness



Zarin D et al JAMA 2019



cohort pubs

no ref standard

pub delay

selective report

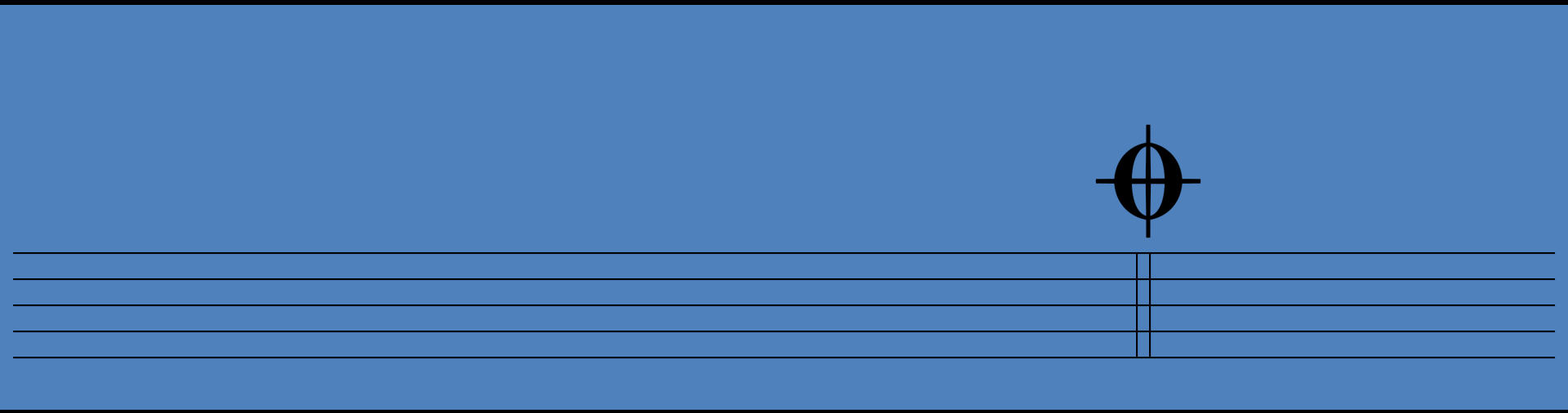
nonpublication

Stem Cell Reports
Article
ISSCR
OPEN ACCESS

Responsible Translation of Stem Cell Research: An Assessment of Clinical Trial Registration and Publications

Moses Fung,[1,2] Yan Yuan,[1] Harold Atkins,[3] Qian Shi,[1] and Tania Bubela[1,*]

2017



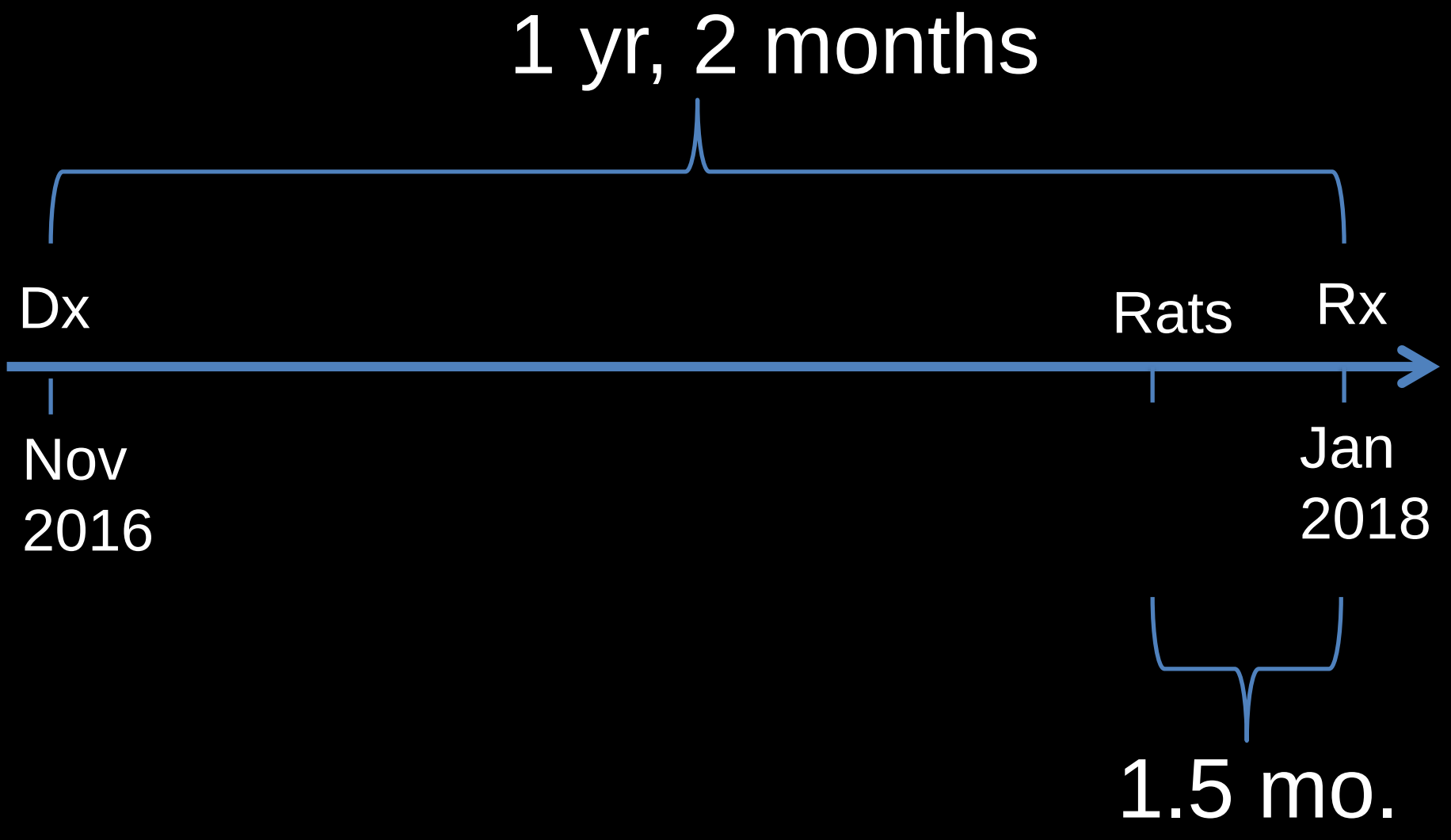
A custommade drug appears to be helping Mila, a 7-year-old born with Batten disease. JULIE AFFLERBAUGH

A tailormade drug developed in record time may save girl from fatal brain disease

By **Jocelyn Kaiser** | Oct. 19, 2018 , 9:00 PM

Science 2019

1. when to begin


1 yr, 2 months
Dx
Rats
Rx
Nov
2016
Jan
2018
1.5 mo.

2. is it therapy ?

IRB reviewed
Informed consent
FDA approved
Intensive baseline
Protocol

~~Peer reviewed~~

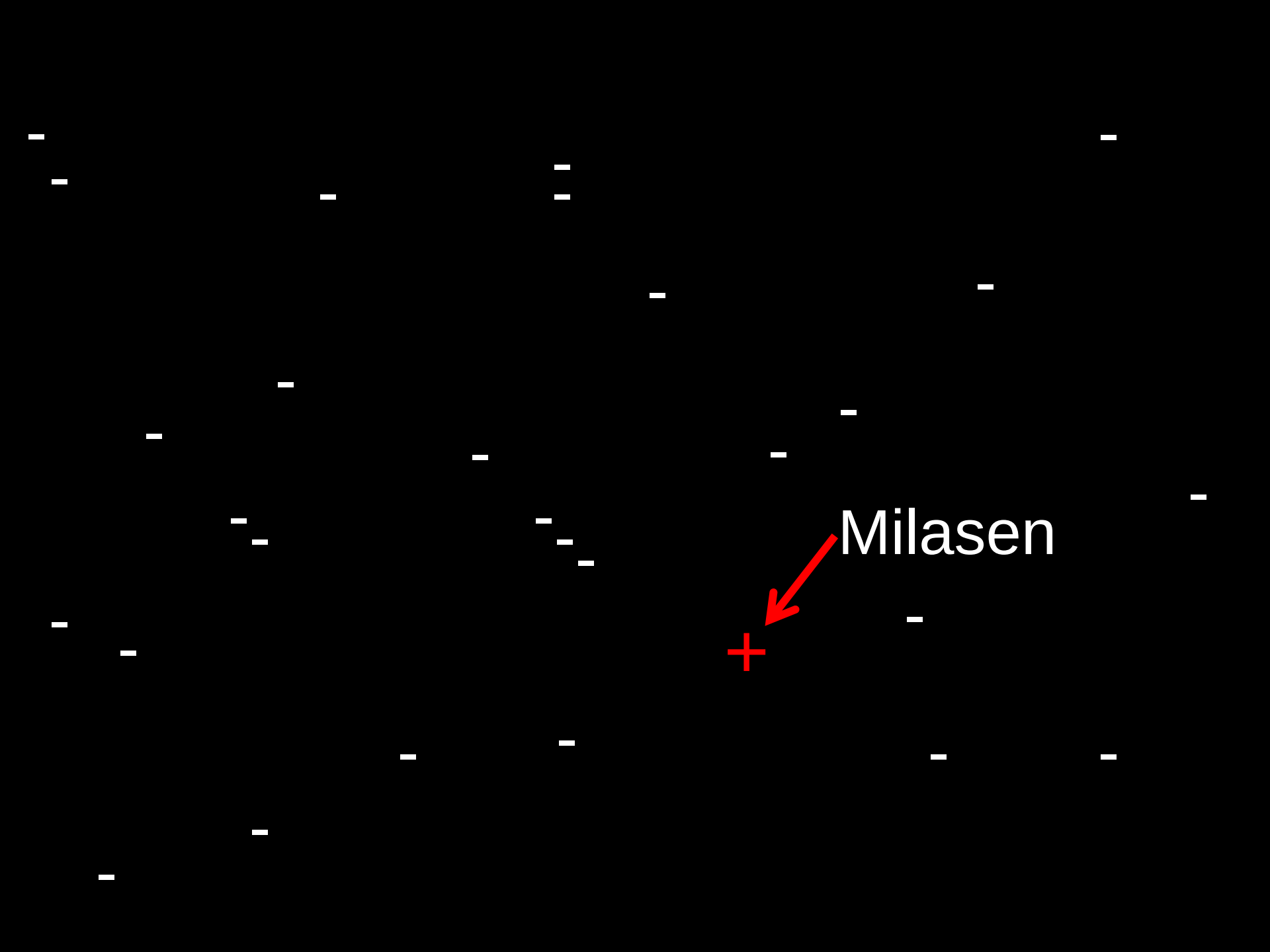
~~Pre-registered~~

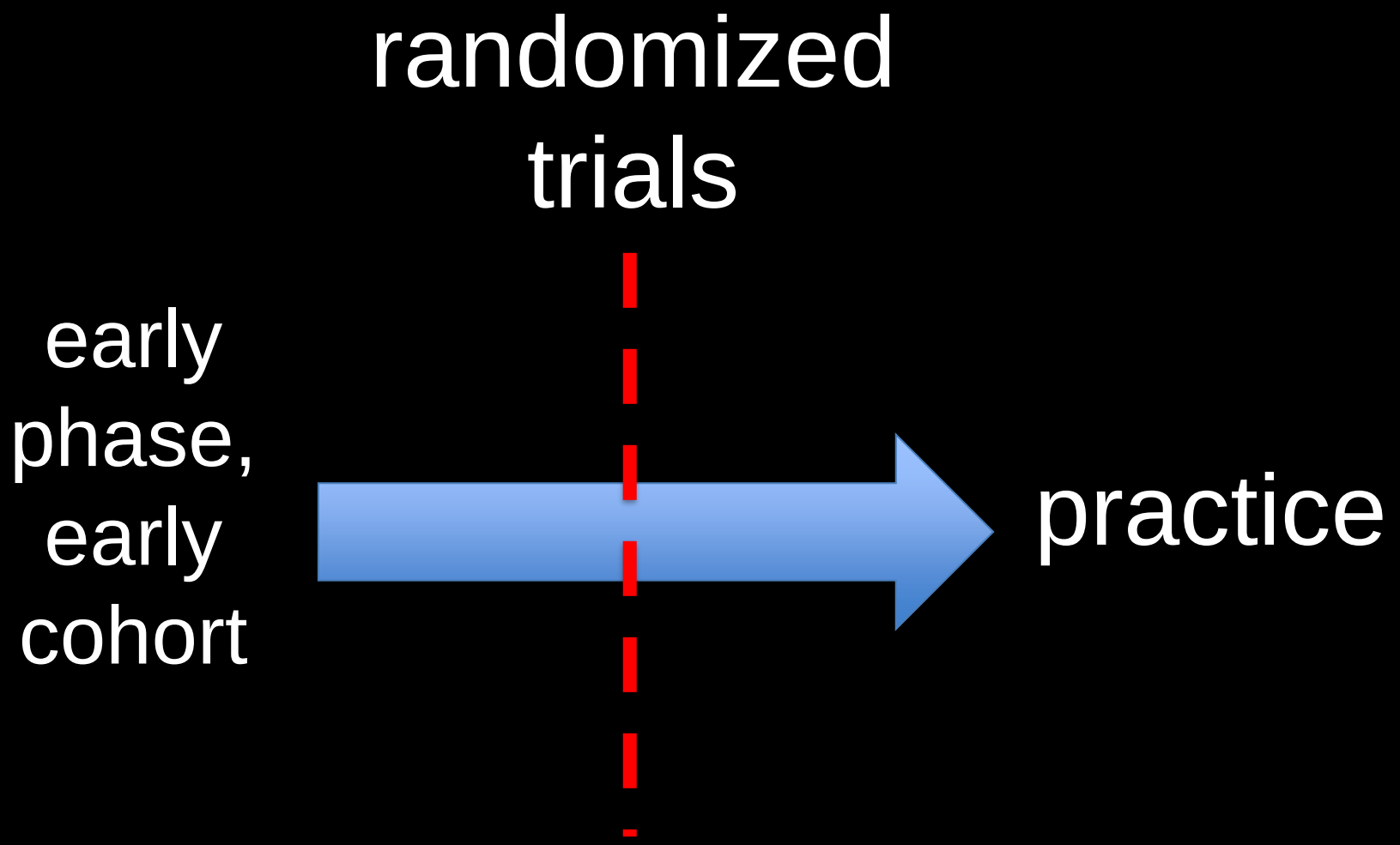
~~Primary endpont~~

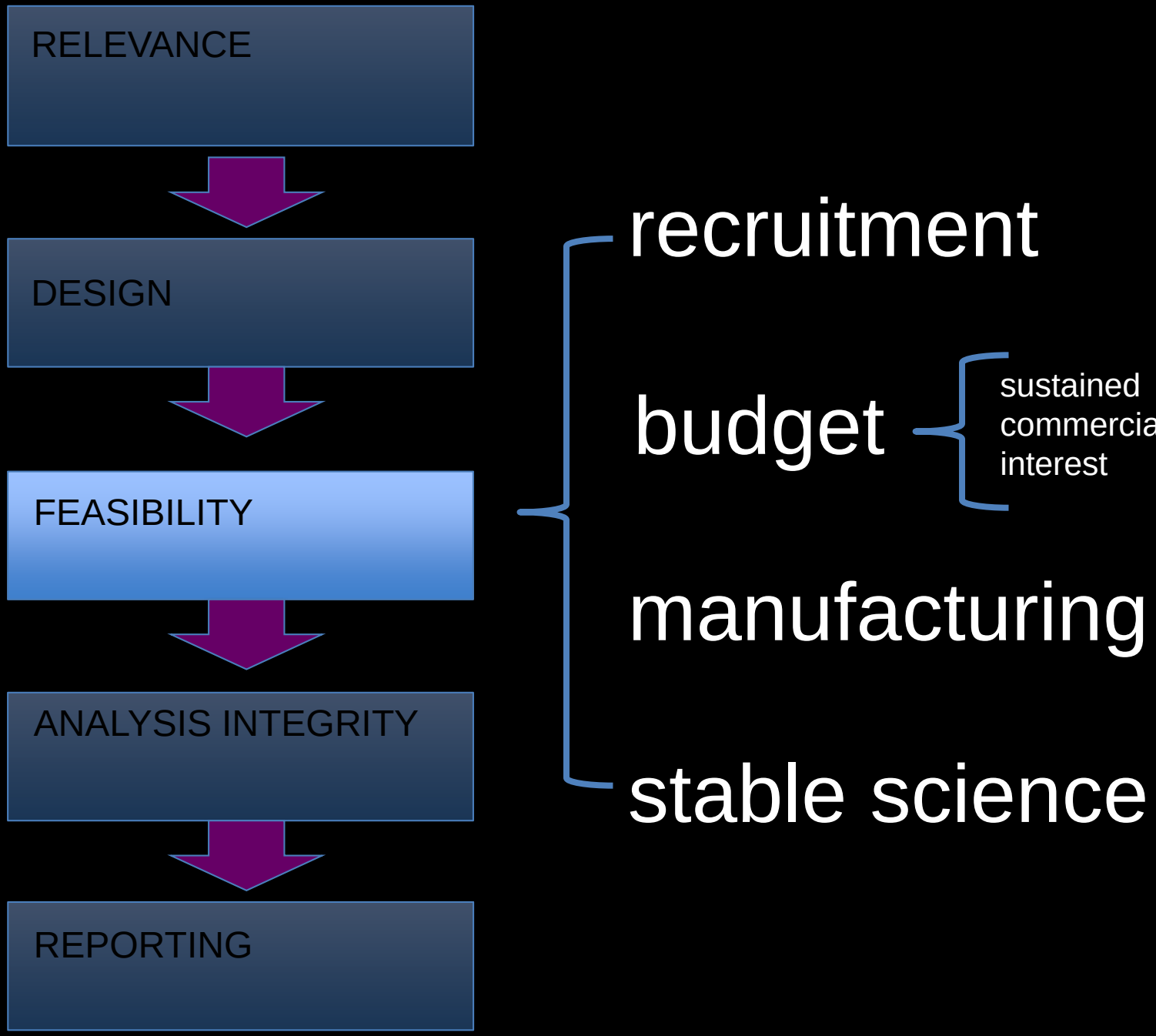
~~No data analysis plan~~

~~Path to license~~

3. informativeness


Milasen

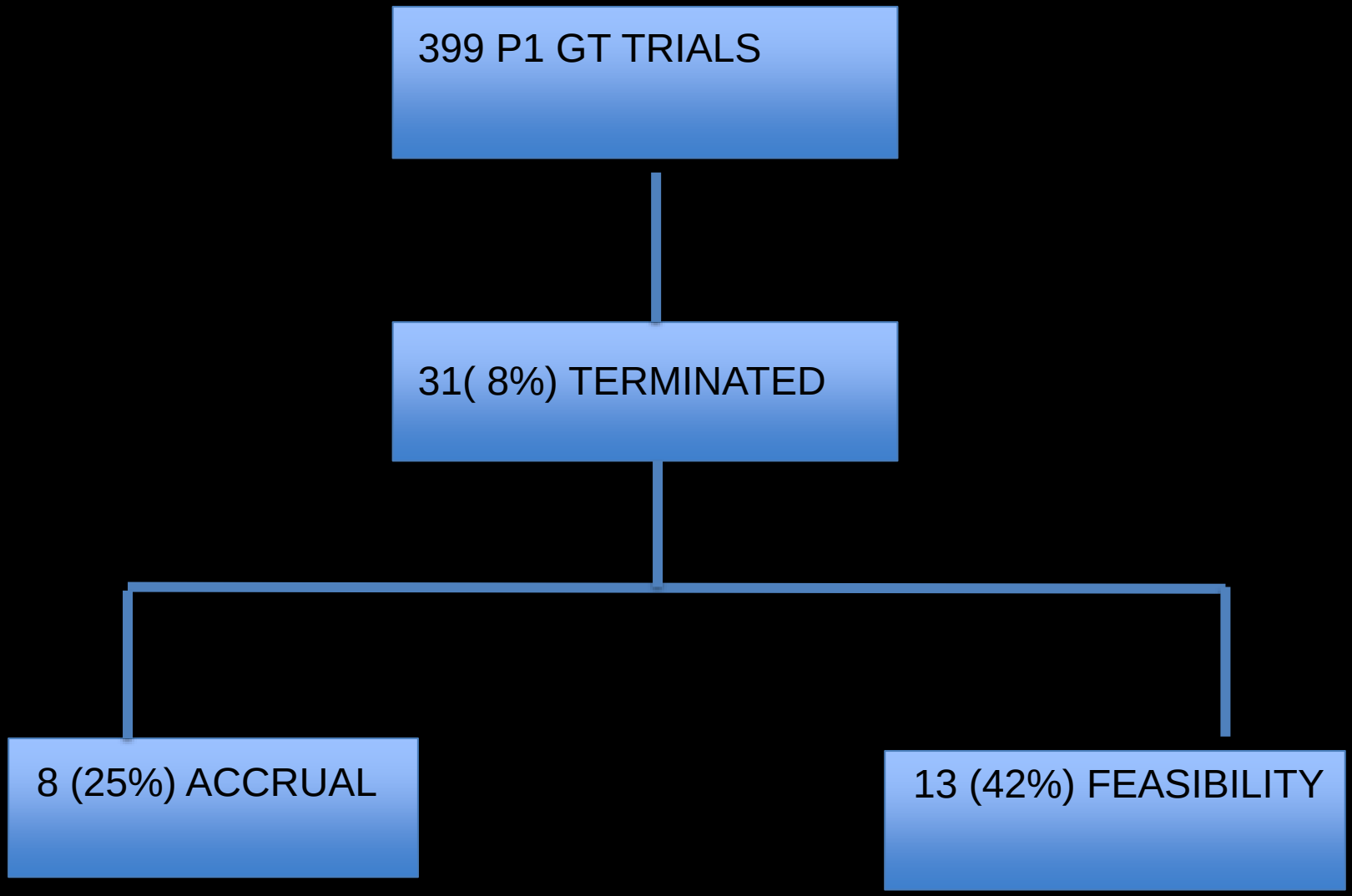

randomized
trials
early
phase,
early
cohort
practice


RELEVANCE
DESIGN
FEASIBILITY
ANALYSIS INTEGRITY
REPORTING
recruitment
budget
sustained
commercial
interest
manufacturing
stable science

Safety and Dose Finding Study of / / / / in Adults with Hemophilia

Estimated enrollment: 18
Actual enrollment: 6

Recruitment Status : Terminated (Sponsor decision; not due to any safety concerns related to [redacted]1.)
First Posted : December 2, 2015
Results First Posted : November 14, 2018
Last Update Posted : November 14, 2018


399 P1 GT TRIALS
31(8%) TERMINATED
8 (25%) ACCRUAL
13 (42%) FEASIBILITY

Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial

Roberto Bolli, Atul R Chugh, Domenico D'Amario, John H Loughran, Marcus F Stoddard, Sohail Ikram, Garth M Beache, Stephen G Wagner, Annarosa Leri, Toru Hosoda, Fumihiro Sanada, Julius B Elmore, Polina Goichberg, Donato Cappetta, Nimesh K Solankhi, Ibrahim Fahsah, D Gregg Rokosh, Mark S Slaughter, Jan Kajstura, Piero Anversa

Summary

Background c-kit-positive, lineage-negative cardiac stem cells (CSCs) improve post-infarction ventricular (LV) dysfunction when administered to animals. We undertook a phase 1 trial (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy [SCIPIO]) of autologous CSCs for the treatment of heart failure resulting from ischaemic heart disease.

Methods In stage A of the SCIPIO trial, patients with post-infarction LV dysfunction (ejection fraction [EF] ≤40%) before coronary artery bypass grafting were consecutively enrolled in the treatment and control groups. In stage B, patients were randomly assigned to the treatment or control group in a 2:3 ratio by use of a computer-generated block randomisation scheme. 1 million autologous CSCs were administered by intracoronary infusion at a mean of 113 days (SE 4) after surgery; controls were not given any treatment. Although the study was open label, the echocardiographic analyses were masked to group assignment. The primary endpoint was short-term safety of CSCs and the secondary endpoint was efficacy. A per-protocol analysis was used. This trial is registered with ClinicalTrials.gov, number NCT00474461.

Findings This study is still in progress. 16 patients were assigned to the treatment group and seven to the control group; no CSC-related adverse effects were reported. In CSC-treated patients who were analysed, LVEF increased from 30·3% (SE 1·9) before CSC infusion to 38·2% (2·2) at 4 months after infusion (p=0·001). By contrast, in seven control patients, during the corresponding time interval, LVEF did not change (30·1% [2·4] at 4 months after CABG *vs* 30·2% [2·5] at 8 months after CABG). Unexpectedly, the salutary effects of CSCs were even more pronounced at 1 year in eight patients (eg, LVEF increased by 12 ejection fraction units [2·1] *vs* baseline, p=0·0007). In the seven treated patients in whom cardiac MRI could be done, infarct size decreased from 32·6 g (6·3) by 7·8 g (1·7; 24%) at 4 months (p=0·004) and 9·8 g (1·3; 30%) at 1 year (p=0·004).

Interpretation These initial results in patients are very encouraging. They suggest that intracoronary infusion of autologous CSCs is effective in improving LV systolic function and reducing infarct size in patients with heart failure after myocardial infarction, and warrant further, larger, phase 2 studies.

Funding University of Louisville Research Foundation and National Institutes of Health.

Introduction

Heart failure is a common, disabling, and expensive disorder. Its prevalence in industrialised nations has reached epidemic levels (ie, about 1 million cases in the UK[1] and nearly 6 million in the USA[2]), and continues to rise. Despite advances over the past 30 years, the prognosis for patients who are admitted to hospital with heart failure remains poor, with a 5-year mortality that is nearly 50%[3]—worse than that for patients with breast or colon cancer.[4] The most common cause of heart failure in the west is ischaemic heart disease.[5] Available treatments do not address the fundamental problem of the loss of cardiac tissue. As a result, interest in attempts to repair the failing heart with the use of stem cells has been increasing, since this approach has the potential to regenerate dead myocardium and thus alleviate the underlying cause of heart failure.[6]

The adult heart contains cardiac stem cells (CSCs) that express the surface receptor tyrosine kinase c-kit.[6,7] These cells are self-renewing, clonogenic, and multipotent—ie, they differentiate into all three major cardiac lineages (myocytes, vascular smooth muscle cells, and endothelial cells).[6,7,8] Results of many studies have shown that transplantation of CSCs in animal models of post-myocardial-infarction heart failure attenuates left ventricular (LV) remodelling and improves LV function in the settings of acute and chronic myocardial infarctions.[6,7,9] Despite these encouraging preclinical results, however, the effects of CSCs in patients have not been investigated. We therefore undertook a phase 1 clinical trial of CSCs in patients with heart failure after myocardial infarction to assess the safety and feasibility of intracoronary CSC infusion and to test the hypothesis that this intervention would improve the contractile

Lancet 2011; 378: 1847–57
Published Online November 14, 2011 DOI:10.1016/S0140-6736(11)61590-0

See Comment page 1827

Divisions of Cardiovascular Medicine (Prof R Bolli MD, A R Chugh MD, J H Loughran MD, Prof M F Stoddard MD, Prof S Ikram MD, S G Wagner MD, J B Elmore MD, N K Solankhi MD, I Fahsah MD, D G Rokosh PhD) and Cardiothoracic Surgery (Prof M S Slaughter MD), and Department of Radiology (G M Beache MD), University of Louisville, Louisville, KY, USA; and Departments of Anesthesia and Medicine and Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (D D'Amario MD, A Leri MD, T Hosoda MD, F Sanada MD, P Goichberg PhD, D Cappetta PhD, J Kajstura PhD, Prof P Anversa MD)

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