The U.S. Regulatory Environment is Evolving to Accommodate a Boom in Gene Therapy Research

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Conflict of Interest Disclosure

The presenter is employed by a for-profit company.

Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP

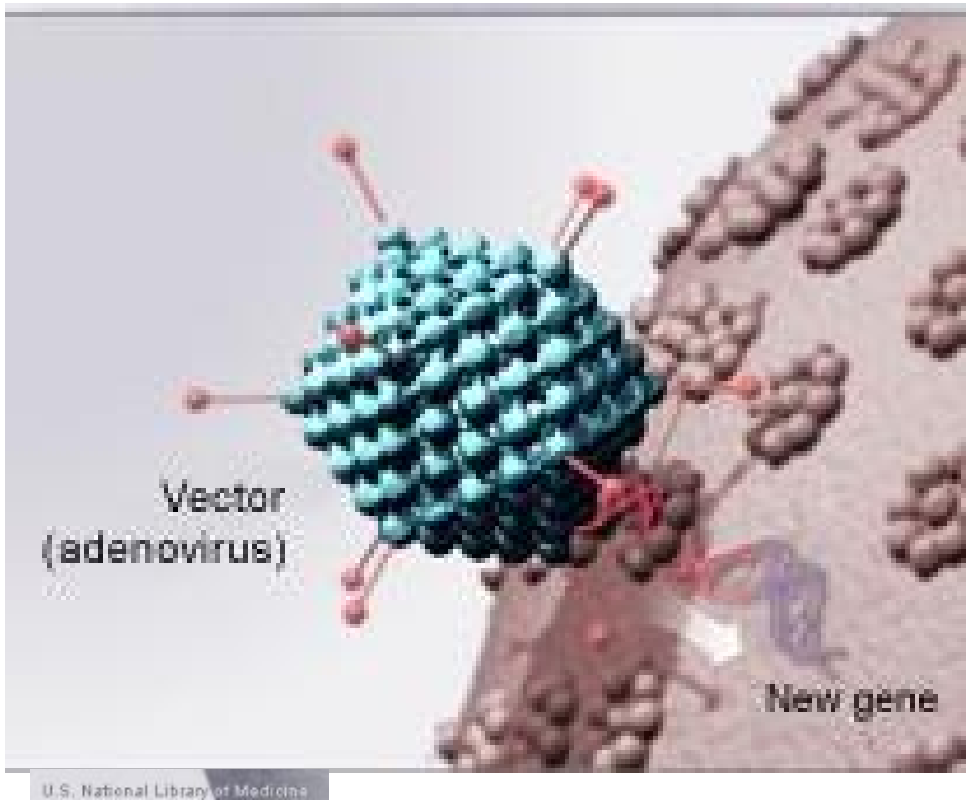
Director of Biosafety Services, Advarra

Agenda

I. The Current State of the Gene Therapy Field
II. Recent Regulatory Changes to Streamline Review of Gene Therapy
    a. Changes at the FDA
    b. Role of the RAC and Revisions to NIH Guidelines
    c. The NIH Single IRB Policy and Changes to Common Rule
III. Strategies for Adapting to the Evolving Regulatory Environment in the U.S.

1. The Current State of the Gene Therapy Field

Defining Gene Therapy Research

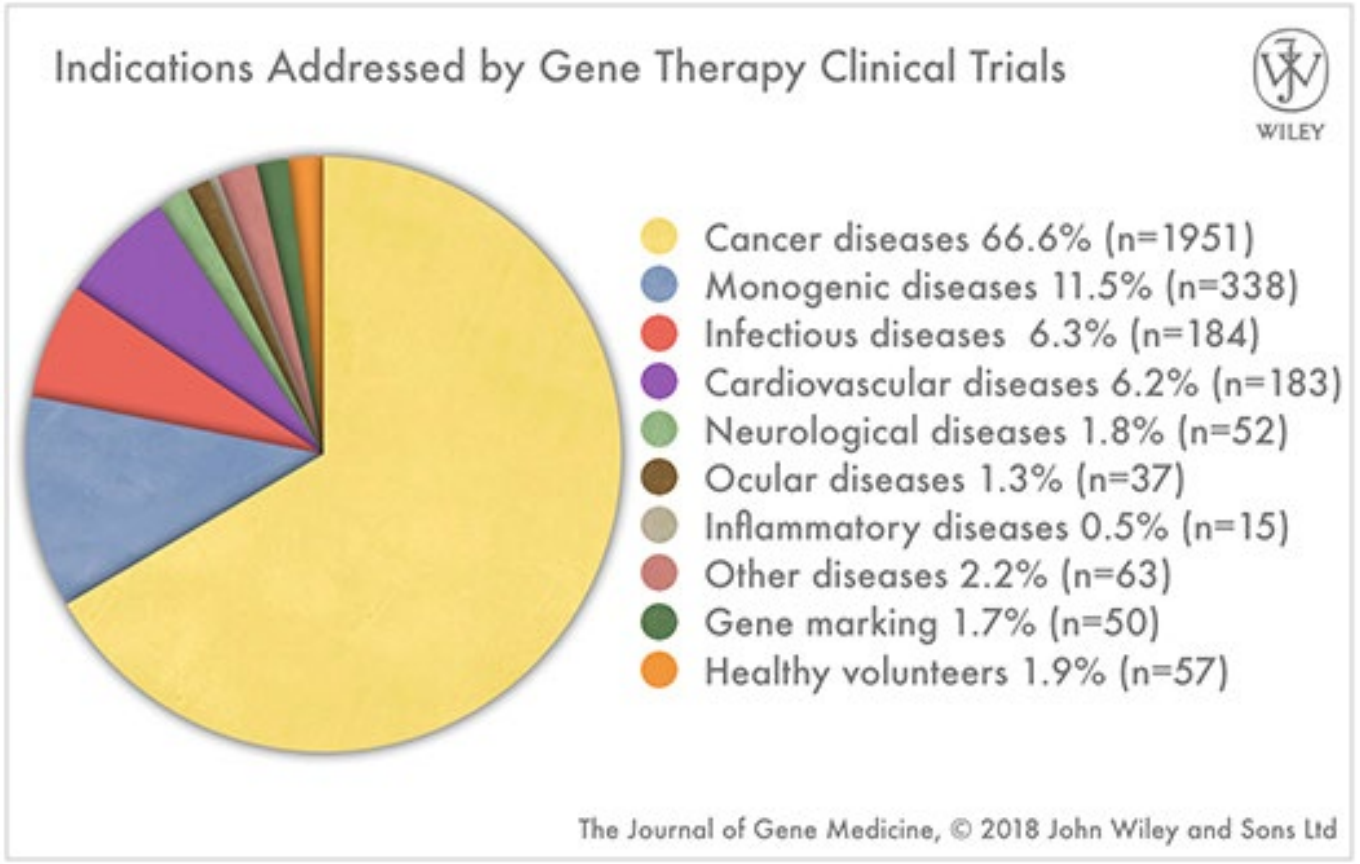


Involves the delivery of genetic material to humans with the goal of compensating for genetic mutations, conferring the capability to produce potentially therapeutic substances, or eliciting immune responses to fight disease.

Genetic material: Recombinant or synthetic nucleic acid molecules

Use of Recombinant & Synthetic Nucleic Acid Molecules in Clinical Trials

- To date, over 2,900* gene therapy clinical trials have been initiated.
- According to clinicaltrials.gov, there are 1084 gene therapy trials currently recruiting or enrolling participants**.
- Recombinant DNA has been utilized in clinical trials for various disease indications.
- Approximately 2/3 of gene therapy studies involve oncology research*.

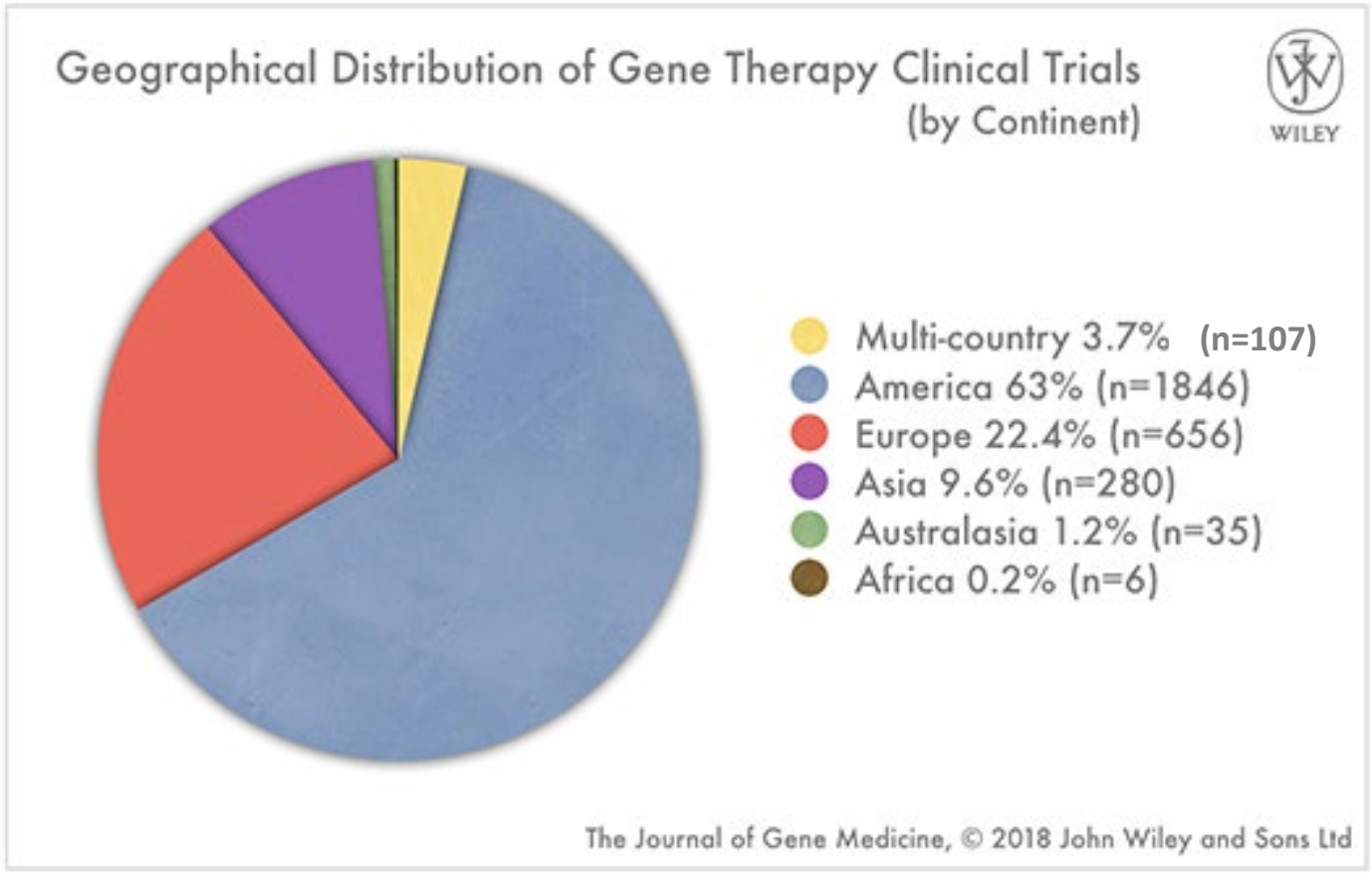


*The Journal of Gene Medicine: Gene Therapy Clinical Trials Worldwide (accessed 11/17/19)

** clinical trials.gov accessed 11/17/19

Use of Recombinant & Synthetic Nucleic Acid Molecules in Clinical Trials

- Most HGT trials take place in the U.S. and Europe
- Marketing approval issued for gene therapy products in China, Europe, the U.S., S. Korea and Australia
- Advances in various technologies are making such studies more common:
  - Human genome project/genomics
  - Genetic engineering
  - Synthetic biology
- Increased trend for tech transfer and startups originating from Academia



*The Journal of Gene Medicine: Gene Therapy Clinical Trials Worldwide (accessed 11/17/19)

Recent FDA Approvals: Gene Therapy Is No Longer Science Fiction

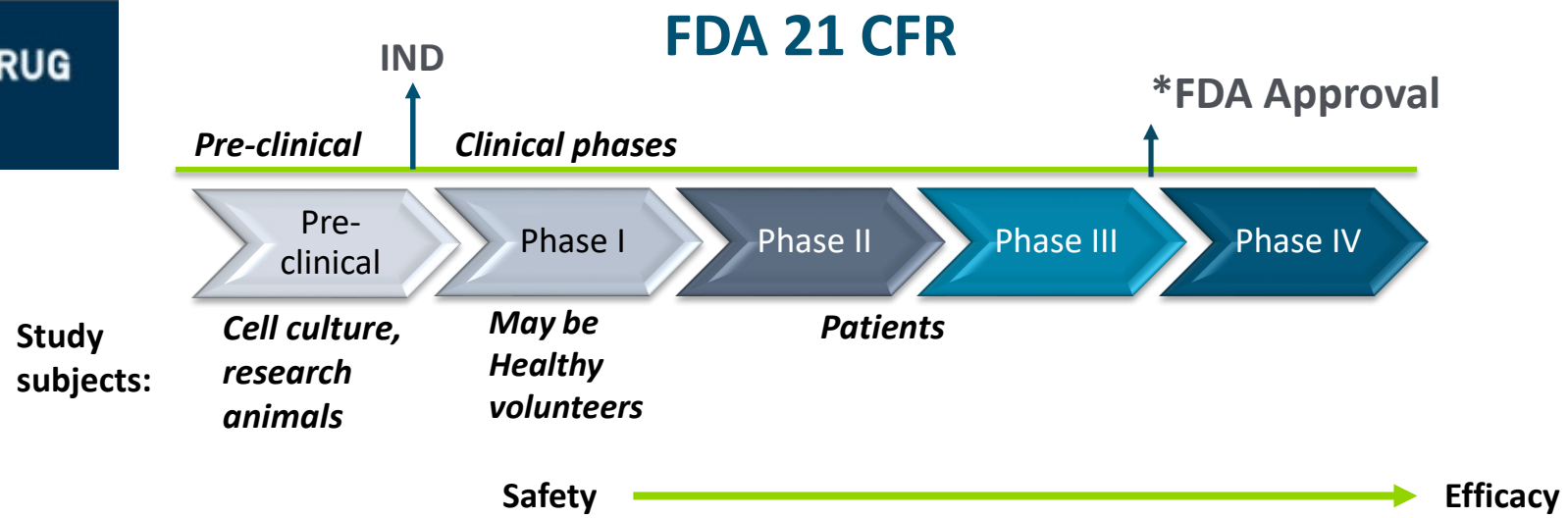
FDA approval of products containing recombinant or synthetic nucleic acids

Name	Manufacturer	Indication	Recombinant DNA	Approval Date
IMLYGIC	Amgen	Melanoma	Herpes simplex virus 1 based oncolytic therapy	October 2015
VAXCHORA	PaxVax	Cholera vaccine (serogroup O1)	Live, attenuated, orally administered *V. cholerae* bacteria, cholera toxin A gene (ctxA) deleted	June 2016
KYMRIAH	Novartis	B Cell Acute Lymphoblastic Leukemia	Chimeric Antigen Receptor (CAR) T Cells	August 2017
YESCARTA	Kite (Gilead)	Non Hodgkins Lymphoma	Chimeric Antigen Receptor (CAR) T Cells	October 2017
LUXTURNA	Spark Therapeutics	Retinitis Pigmentosa	AAV vector delivering RPE65	December 2017
DENGVAXIA	Sanofi Pasteur	Dengue serotypes 1-4	Yellow fever 17D204 vaccine strain encoding pre-membrane (prM) and envelope (E) proteins from dengue 1-4	May 2019
ZOLGENSMA	Novartis	Spinal Muscular Atrophy	AAV vector delivering the *SMA1* gene	May 2019

FDA Oversight of Clinical Trials

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION



Phase	I	II	III	IV
No. of Subjects	20-100	Hundreds	300-3,000	Several Thousand

*FDA Approval

IND: Investigational New Drug, Phase I – IV
IRB: Institutional Review Board
BLA: Biologics License Application

Source: FDA.gov

Many More FDA Approvals for Gene Therapy Products Are Expected

- There are currently 298 Phase III gene therapy trials listed on clinicaltrials.gov. (11/17/2019)

https://www.biospace.com/article/gottlieb-at-bio-2018-40-gene-therapy-approvals-by-2022/

Gottlieb at BIO 2018: 40 Gene Therapy Approvals by 2022

Published: Jun 07, 2018 | By Mark Terry

Dr. Scott Gottlieb / Albert H. Teich / Shutterstock

As the **2018 BIO International Convention** wraps up in Boston today, it kicked off with a fireside chat with **Dr. Scott Gottlieb,** Commissioner of the U.S. Food and Drug Administration (FDA). Gottlieb was interviewed by **Jim Greenwood,** president and chief executive officer of BIO.

Applied Biosafety

www.absa.org Volume 24, Number 3, September 2019

The Biotech Death of Jesse Gelsinger

By SHERYL GAY STOLBERG NOV. 28, 1999 The New York Times Magazine

Gene Therapy Death Prompts Review of Adenovirus Vector

Eliot Marshall

+ See all authors and affiliations

Science 17 Dec 1999:
Vol. 286, Issue 5448, pp. 2244-2245
DOI: 10.1126/science.286.5448.2244

FDA halts gene therapy trials after leukaemia case in France

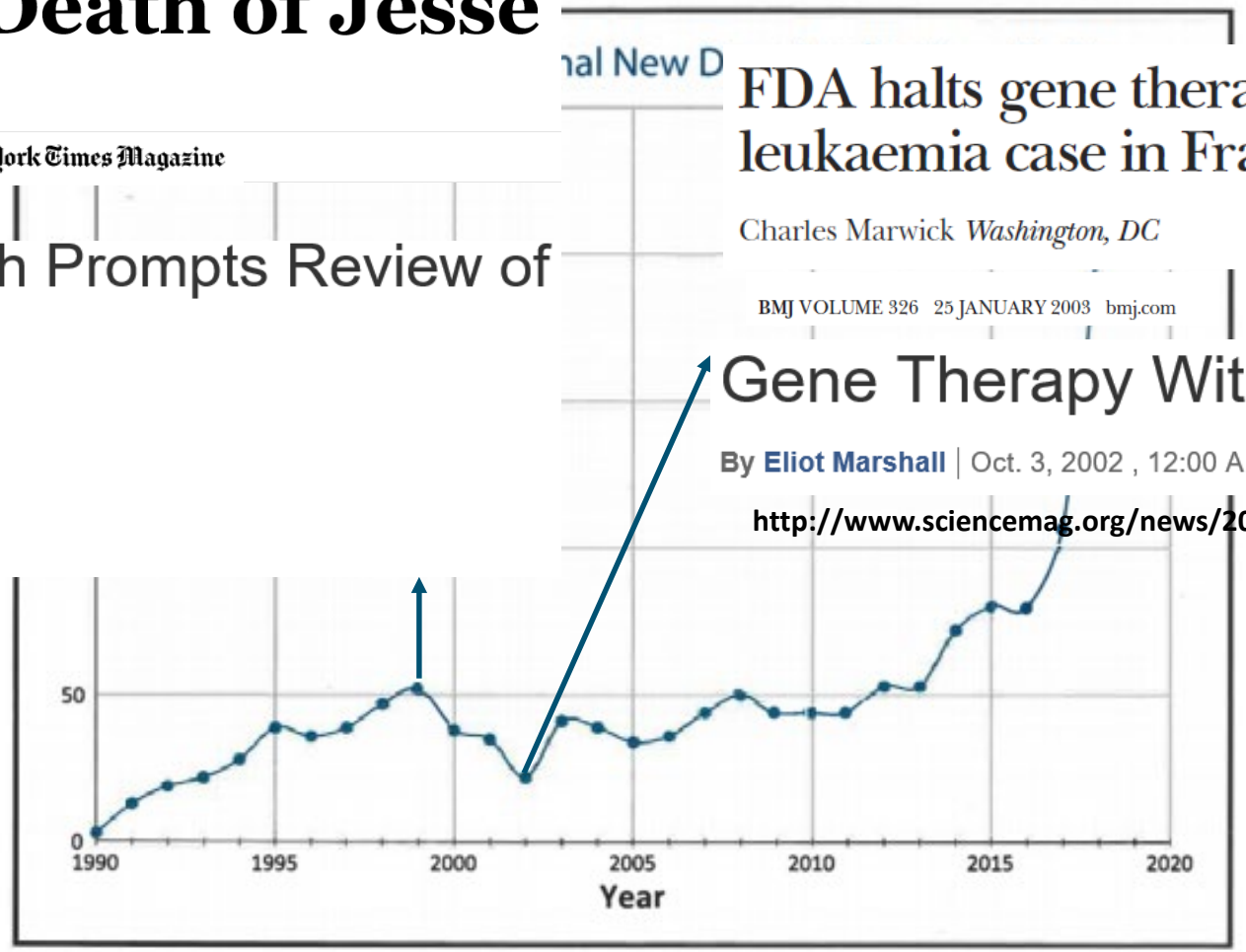
Charles Marwick *Washington, DC*

BMJ VOLUME 326 25 JANUARY 2003 bmj.com

Gene Therapy With Retroviruses Halted

By **Eliot Marshall** | Oct. 3, 2002 , 12:00 AM

http://www.sciencemag.org/news/2002/10/gene-therapy-retroviruses-halted



Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER)

Source: Eisenman, *Applied Biosafety,* 2019

FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mu… specific gene

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For Immediate Release December 19, 2017

YEAR IN REVIEW CANCER, IMMUNE SCIENCE, 2017 TOP 10

Approval of gene therapies f… two blood cancers led to an ‘explosion of interest’ in 2017

CAR-T cell therapy treats patients for whom other therapies haven’t worked

BY LAUREL HAMERS 8:27AM, DECEMBER 13, 2017

https://www.sciencenews.org/article/car-t-cell-gene-therapy-top-science-stories-2017-yir

FDA Approves First Oncolytic Virus Therapy

Imlygic for Melanoma

Oncology Times: December 10, 2015 - Volume 37 - Issue 23 - p 36
doi: 10.1097/01.COT.0000475724.97729.9e
FDA Updates

iosafety

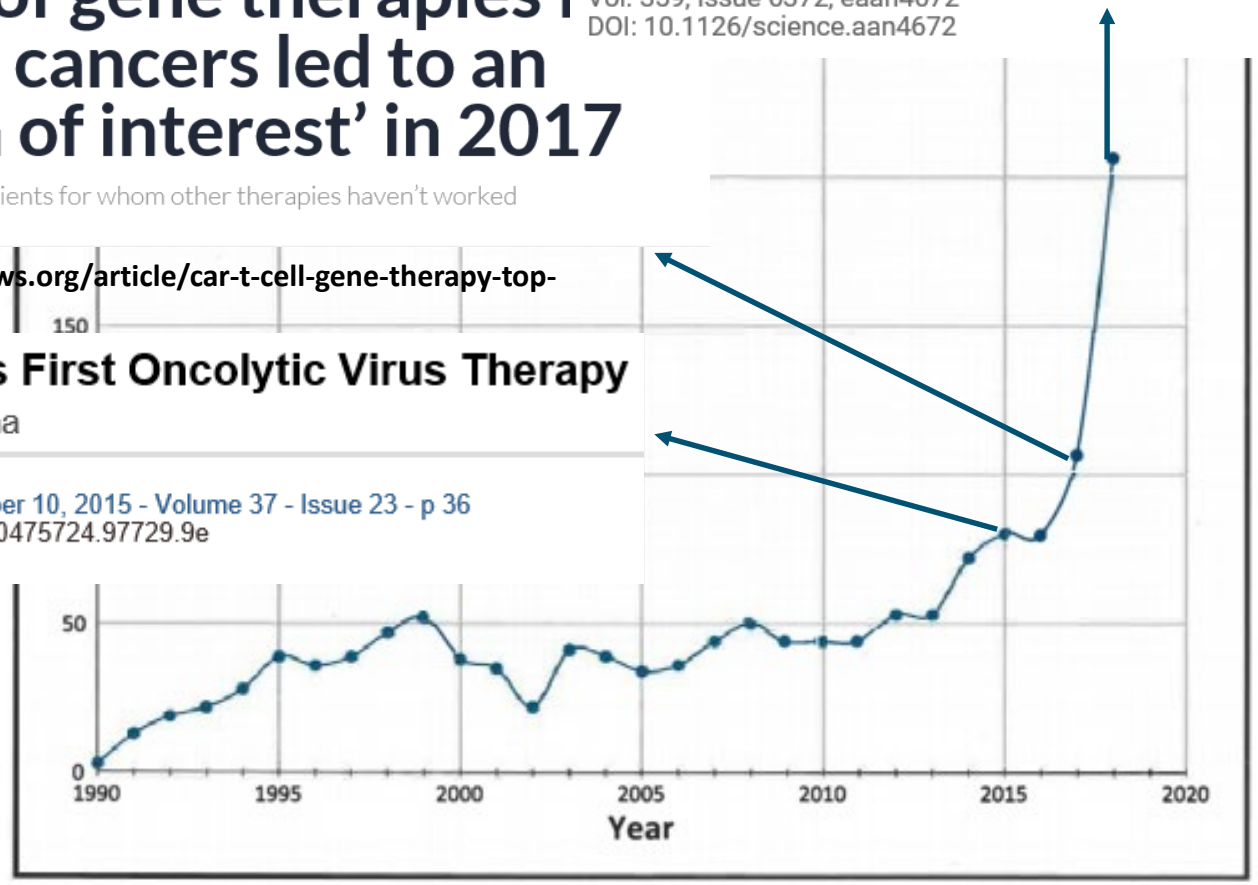
REVIEWS | REVIEW

Gene therapy comes of age

Cynthia E. Dunbar[1,*], Katherine A. High[2], J. Keith Joung[3], Donald B. Kohn[4], Keiya Ozawa[5], Michel Sadelain[6,*]

+ See all authors and affiliations

Science 12 Jan 2018:
Vol. 359, Issue 6372, eaan4672
DOI: 10.1126/science.aan4672

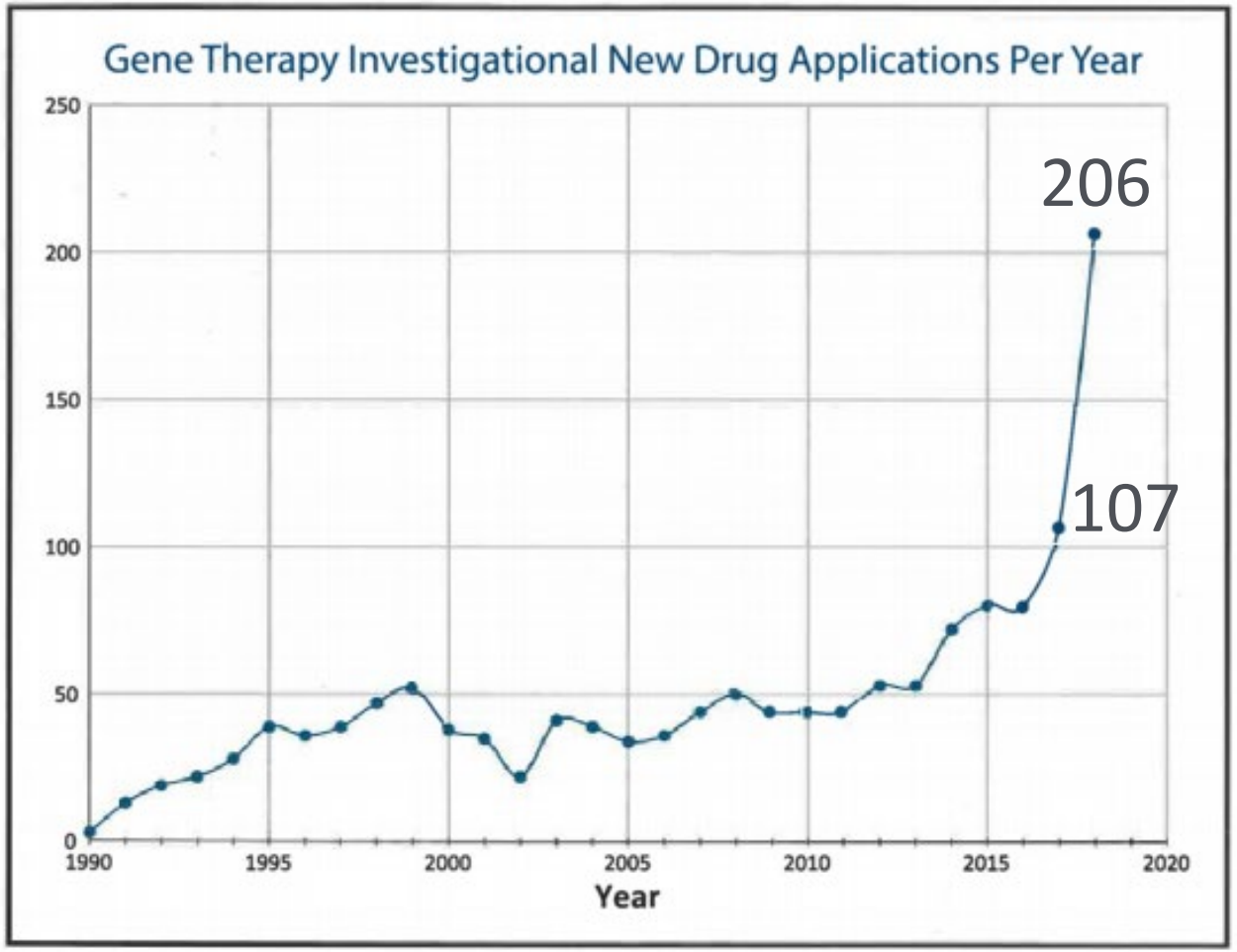


Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER)

Source: Eisenman, *Applied Biosafety,* 2019

Applied Biosafety
www.absa.org
Volume 24, Number 3, September 2019

*2019: 300+ expected



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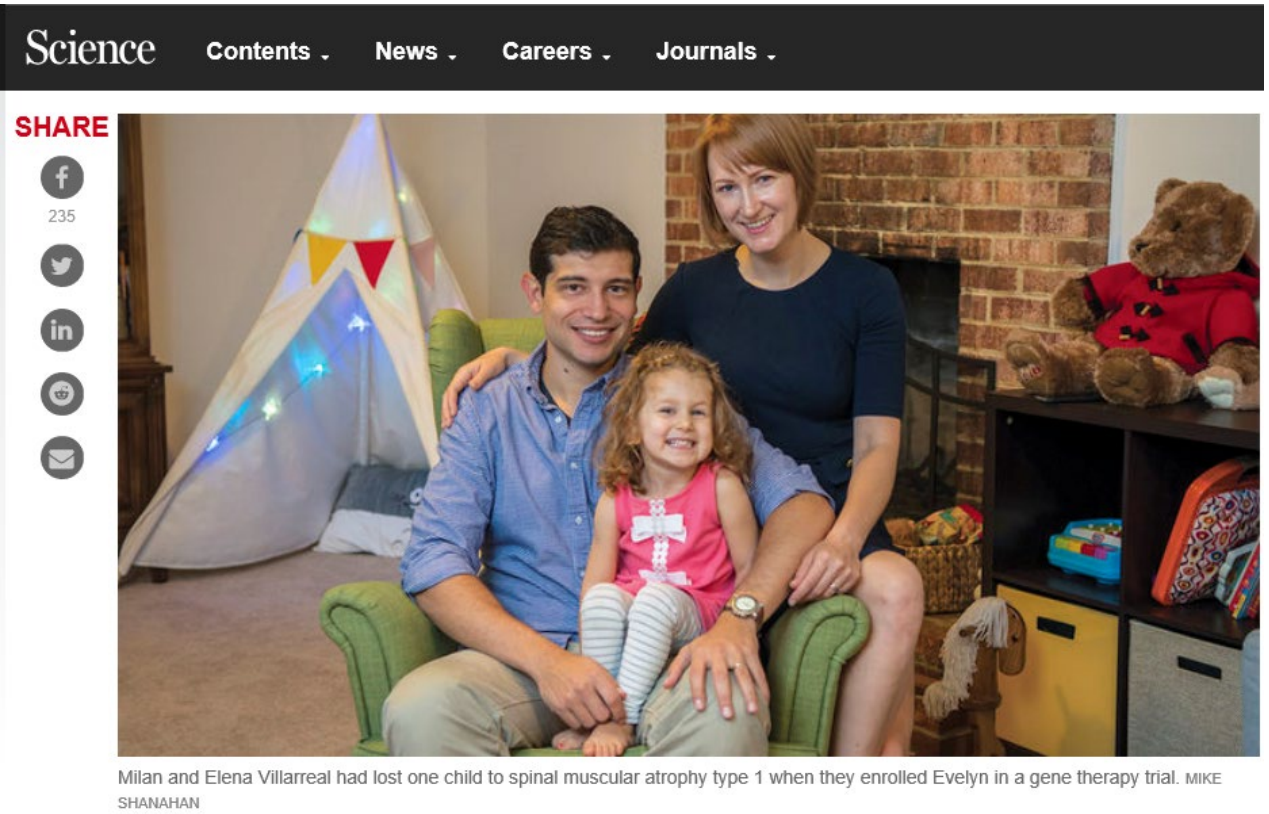
Success Stories



Milan and Elena Villarreal had lost one child to spinal muscular atrophy type 1 when they enrolled Evelyn in a gene therapy trial. MIKE SHANAHAN

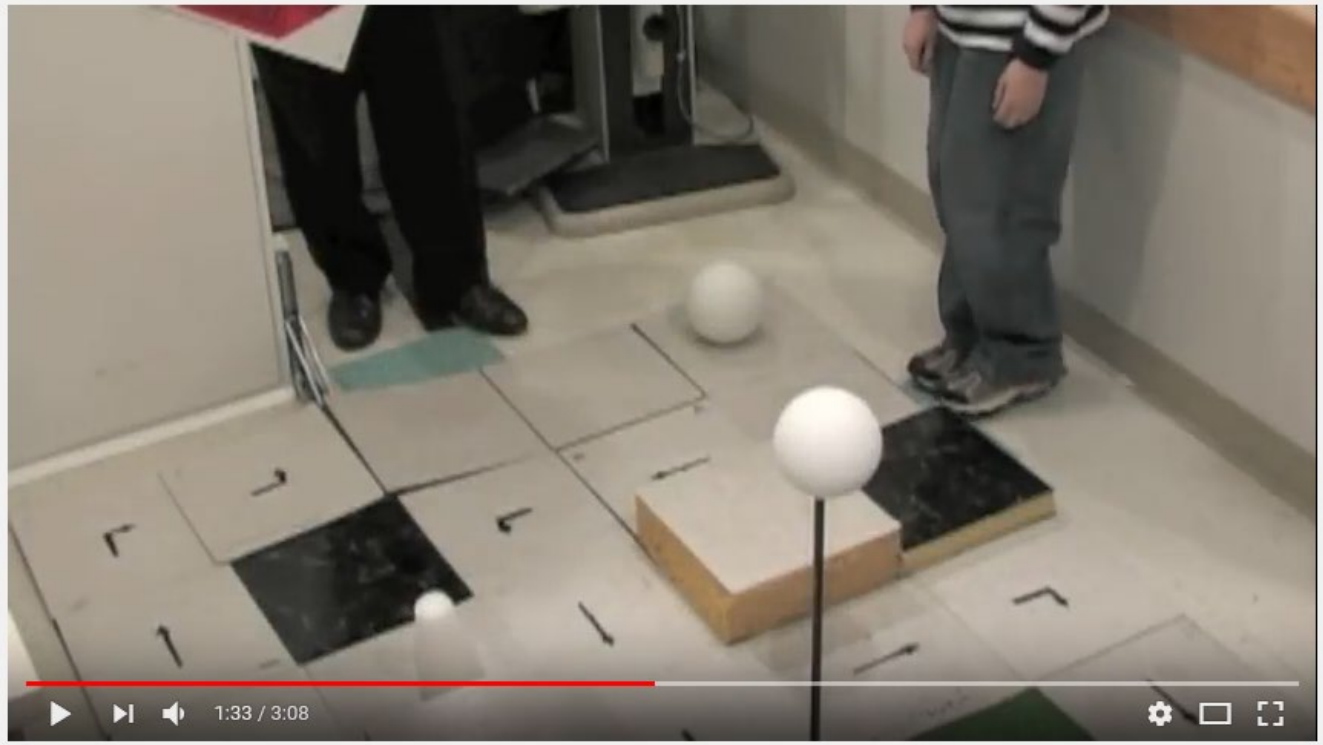
spinal muscular atrophy type 1 (SMA1)
Recessive disease that gradually paralyzes and kills infant prior to 2 years of age.
The Villareal family already had one daughter die at 15 months from SMA
2nd daughter Evelyn participated in the clinical trial at 8 weeks of age.
She is now 3 and pictured running, never seen before in SMA1 patients

Evelyn Villarreal, treated for spinal muscular atrophy type 1 with a new gene therapy, is nearly 3. Few children with her condition reach age 2. MIKE SHANAHAN

***Science*, Nov. 1, 2017**
https://www.sciencemag.org/news/2017/11/gene-therapy-s-new-hope-neuron-targeting-virus-saving-infant-lives

Success Stories

Jack Hogan, 7 YO boy with Retinitis Pigmintosa
Recessive RPE65 gene causes blindness in adolescence



Jean Bennett on gene therapy as a treatment for blindness | Charlie Rose

Source: https://www.youtube.com/watch?v=lAo9Jdqrdlo

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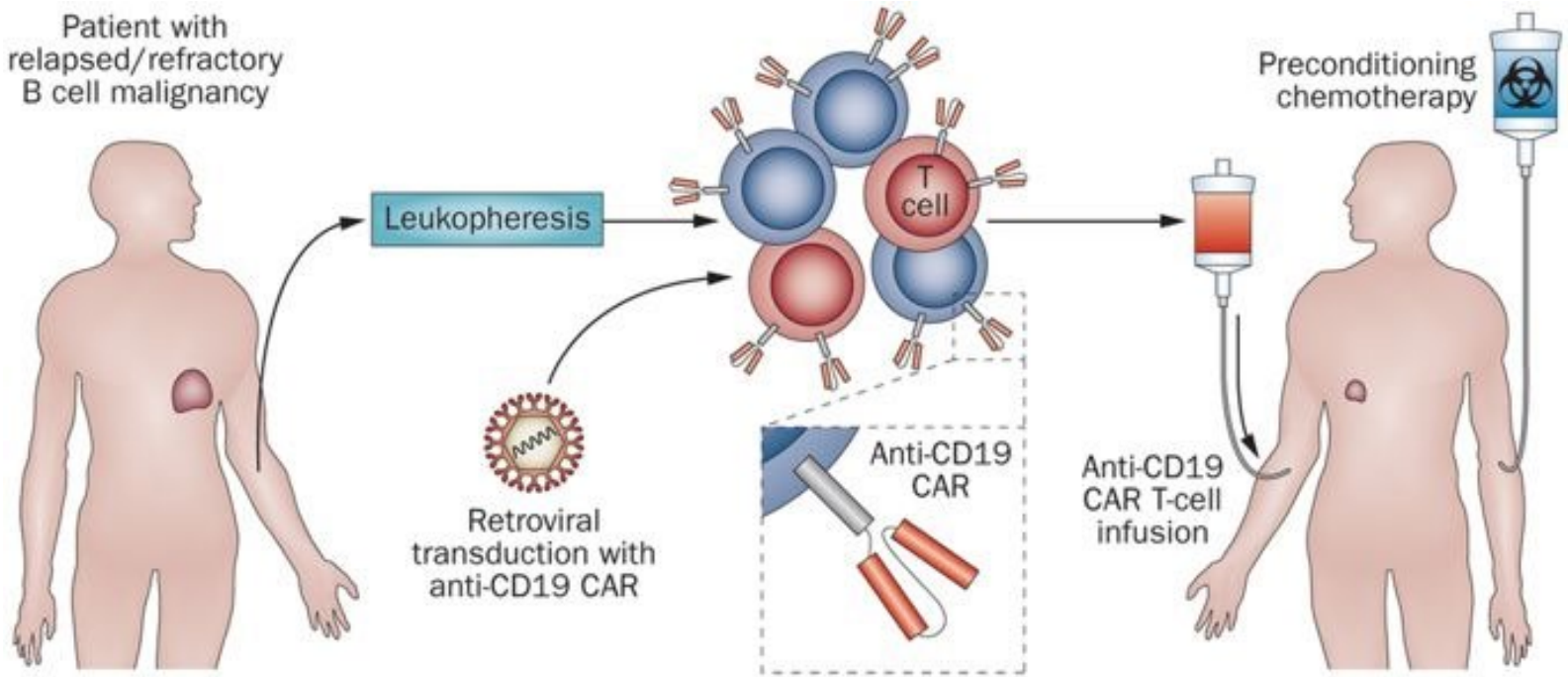
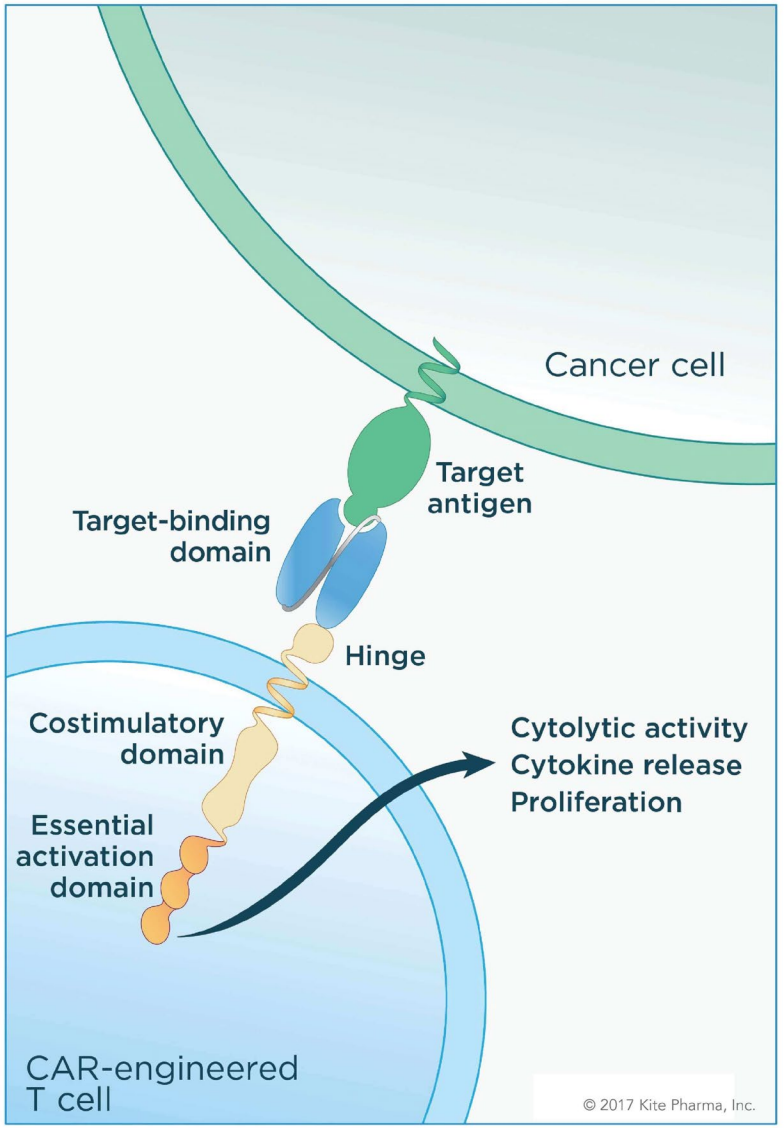


Nature Reviews Clinical Oncology **volume 11**, pages 685–686 (2014)

CHIMERIC ANTIGEN RECEPTOR (CAR)



2. Recent Regulatory Changes to Streamline Review of Gene Therapy Research

FDA Expects a Boom in Gene Therapy Research

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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News & Events

Home > News & Events > Newsroom > Press Announcements

FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies

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For Immediate Release

January 15, 2019

- 50 additional clinical reviewers for cell and gene therapy
- 200 Investigational New Drug applications per year by 2020
- 10 to 20 approvals each year by 2025.

"The activity reflects a turning point in the development of these technologies and their application to human health. It's similar to the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens."

Source: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm

The RMAT Designation for Expedited Review

The 21st Century Cures Act created a **Regenerative Medicine and Advanced Therapies (RMAT)** designation to facilitate expedited review by the FDA.

a. The drug is a regenerative medicine therapy, which is defined as a **cell therapy, therapeutic tissue engineering product, human cell and tissue product**, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;

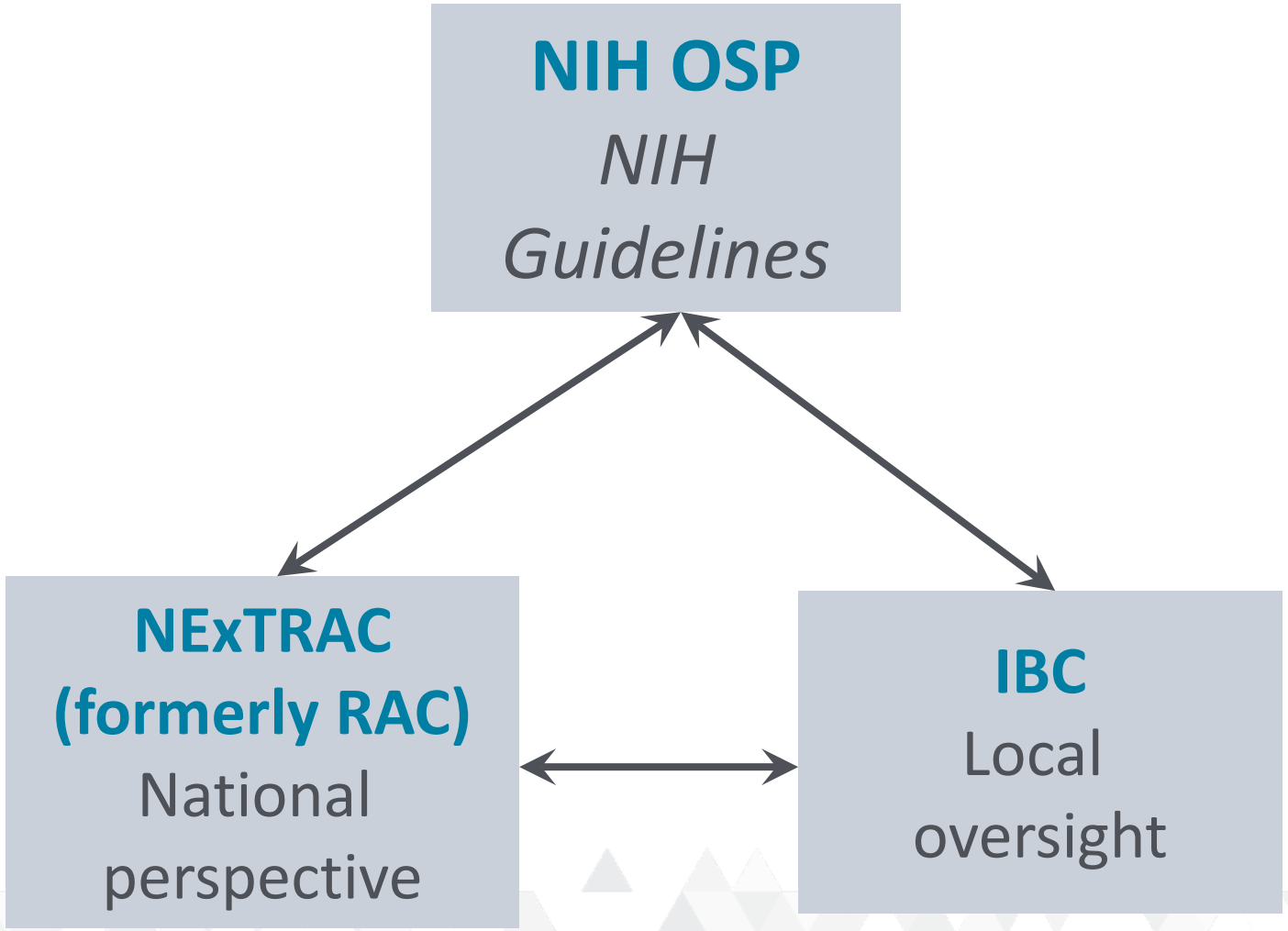
b. **The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and**

c. **Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition**

"…gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy."

Source: U.S. FDA, Vaccines, Blood and Biologics Regenerative Medicine Advanced Therapy Designation

Structure of Oversight for Recombinant DNA Research



Evolution of RAC Review of Human Gene Transfer

1980s

All HGT submitted to NIH for RAC Review or Exemption

April 2016

IBC and IRB make RAC Determinations. Studies registered with NIH OSP.

*3 of 275 studies warranted RAC review

August 2018

NIH no longer accepts IBC/IRB RAC determinations.

RAC no longer reviews individual protocols.

RAC announced as NExTRAC

April 2019

New version of NIH Guidelines

Appendix for HGT removed

HGT covered under Section III-C-1


THE NIH DIRECTOR

The NIH Director

Photo Gallery

Congressional Testimonies

Advisory Groups

Video & Sound Gallery

Articles

August 16, 2018

Statement on modernizing human gene therapy oversight


The NEW ENGLAND JOURNAL of MEDICINE

The Next Phase of Human Gene-Therapy Oversight

Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.

NIH Single IRB Policy & Change to Common Rule Require Single IRB Review

NIH Single IRB Policy for Multi-Site Research

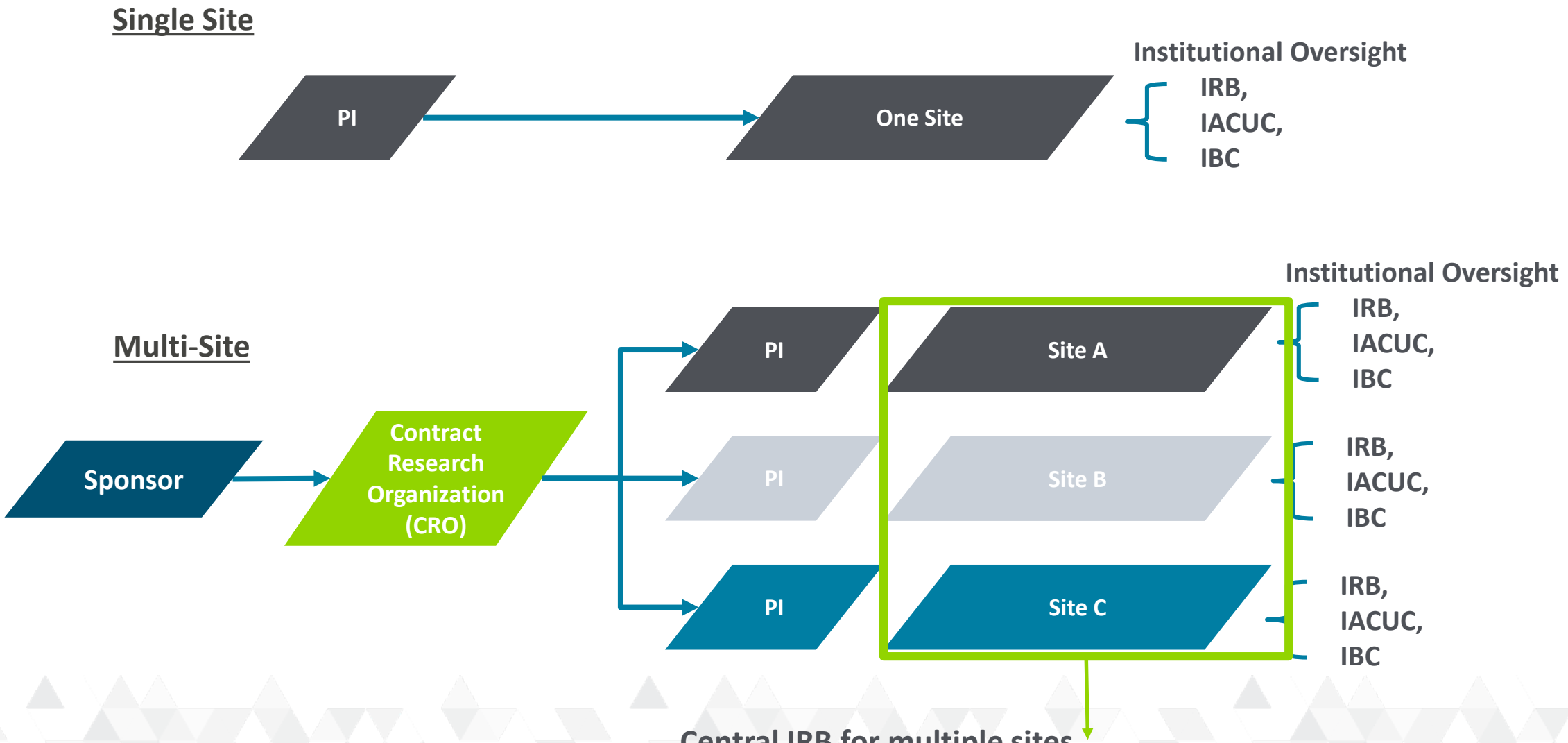
- Applicable to:
  - Domestic sites funded by the NIH
  - Conducting the same protocol involving non-exempt human subjects
- Applicants expected to include a plan for the use of a single IRB in their NIH grant applications by **January 25, 2018**

The Common Rule is the baseline standard of ethics for U.S. government funded research on human subjects. Found in: 45 CFR 46

Revision to the Common Rule: **Single IRB-of-Record (sIRB)** – IRB oversight for most federally funded collaborative research projects located in the US will be required to use a single IRB **starting January 20, 2020**

3. Strategies for Adapting to the Evolving Regulatory Environment in the US

Single Site vs Multisite Clinical Trials



How do we accommodate?

- NIH Single IRB policy and the upcoming changes to the Common Rule requiring multi-site studies to utilize **single IRBs**?
- NIH Guidelines' focus on **local IBC oversight**?

Strategies for Handling Federally Funded Multi-Site Gene Therapy Studies

1. Utilize a single IRB from an institution with the bandwidth to service additional sites

- Creation of a consortium of IRBs
- This approach minimizes or eliminates crosstalk between the additional sites' IBCs and the single IRB
- Some sites may lack IBCs or the expertise to review gene therapy studies

2. Utilize a commercial IRB with an associated IBC service

- Standardization of IBC forms, policies and procedures across sites/institutions to minimize turnaround times
- Gene therapy research expertise readily available for all sites
- Maintains crosstalk between the single IRB and all sites utilizing the IBC service

Questions?

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The Common Rule

The Common Rule is the baseline standard of ethics for U.S. government funded research on human subjects.
Found in: 45 CFR 46

Nearly all U.S. academic institutions hold their researchers to these statements of rights regardless of funding.

Requirements for:
- **Assuring compliance**
- Obtaining and documenting **informed consent**
- **Institutional Review Board (IRB)** membership, function, operations, review of research, and record keeping.

Additional **protections for certain vulnerable research subjects**:
- Subpart B: pregnant women, in vitro fertilization, and fetuses
- Subpart C: prisoners
- Subpart D: children.