Expanded Access to Investigational Drugs and Biologics

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ge²p² global foundation
governance, ethics, evidence, policy, practice

FDLI · November 19, 2020

FDA Drug Approval

- Most effective way to get meaningful therapy to the greatest number of patients
  - Based upon evidence from rigorous clinical trials
    - Demonstrated to be "safe and effective"
  - Adequate labeling to guide use and predict and manage potential risks
  - Third party reimbursement


AMERICANS AGREE:
"BROAD PUBLIC SUPPORT FOR ACCESS TO EXPERIMENTAL MEDS."
– POLITICO, 3/12/18
SPONSORED BY AMERICANS FOR PROSPERITY

What is Expanded Access?

- Use of an investigational drug or biologic **to treat a patient** with a serious disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition
  - Intent is clearly **treatment**

- Contrast with investigational drug in a **clinical trial** where the primary intent is **research**
  - Systematic collection of data with the intent to analyze it to learn about the drug

What is Expanded Access?

- A pathway created and regulated by the Food and Drug Administration (FDA) that **allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions** who have exhausted approved therapy options, and cannot participate in a clinical trial

Drugs, as used here, includes biologics. There are separate, but similar regulations that apply to medical devices.

Expanded Access Programs (EAP)

Are Considered Options of Last Resort

- Logical Hierarchy of Access -

Approved Drugs

Studied and characterized

Labeled

Broadest Availability

3rd party Reimbursement

Clinical Trials

Provide necessary data to determine safety & effectiveness

Most efficient path to market and broadest availability

Expanded Access

Represent opportunity when other options exhausted

Goal is access for treatment

What's in a Name?

A sampler of confusing nomenclature

- Treatment Access
- Compassionate Use
- Named Patient Program
- Pre-approval access
- Pre-launch Access
- Managed Access Program
- ★ Expanded Access

Expanded Access Programs (EAP)

Companies own their products –
They have to be on board

FDA cannot mandate access

Historical Underpinnings

- History of facilitating access to investigational therapies reaches back to 1970s
  - Cardiovascular - metoprolol, nifedipine
  - HIV - pentamadine, AZT
  - Oncology (Group C drugs)

- First official regulatory recognition in 1987 when IND regs were revised to provide access for a broad patient population under a Treatment IND/Protocol (21 CFR 312.34)

- Implicit recognition of treatment use for individuals for emergency use (21 CFR 312.36), though no specific criteria or requirements described

Why Expanded Access?

- Not all patients can wait for approved drugs
  - No effective therapy for condition
  - Exhausted approved options
  - Intolerant of approved products
  - Cannot participate in clinical trials

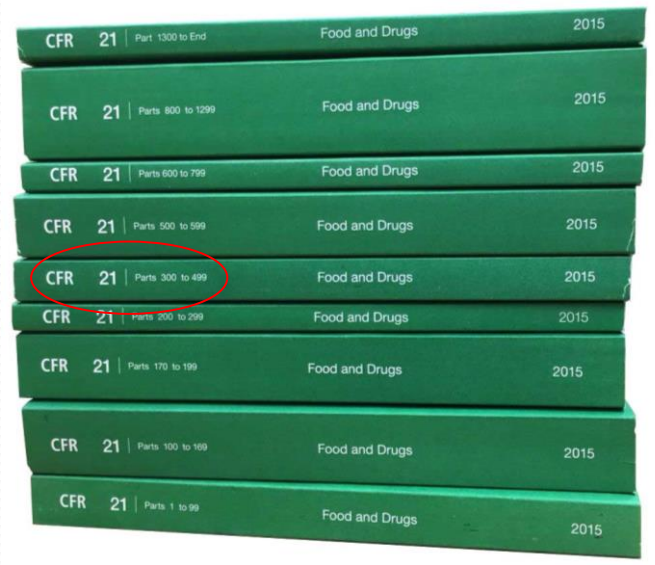
☞ Expanded access allows access to unapproved/investigational drugs that might potentially provide benefit, when a company is able and willing to provide it, and ethical protections are in place (IRB/informed consent)

FDA Published Revised Regulations

2009

21 CFR 312 / IND Regulations

- **<u>Subpart I</u>** consolidates treatment use into a separate subpart of the IND regulations containing all relevant information in one place



21 CFR 312 Subpart I

- Describes the **general criteria** applicable to all categories of access, and additional criteria that must be met for each access category
- Describes **requirements for submission**
- Describes the **safeguards** applicable to EAPs (e.g., informed consent, IRB review, reporting requirements)

Requirements shared by all EAPs

21 CFR 312.305

- Serious or immediately life threatening illness or condition
- No comparable or satisfactory alternative therapy
- Potential benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated
- Providing the drug will not interfere with or compromise development for the expanded access use

Definitions

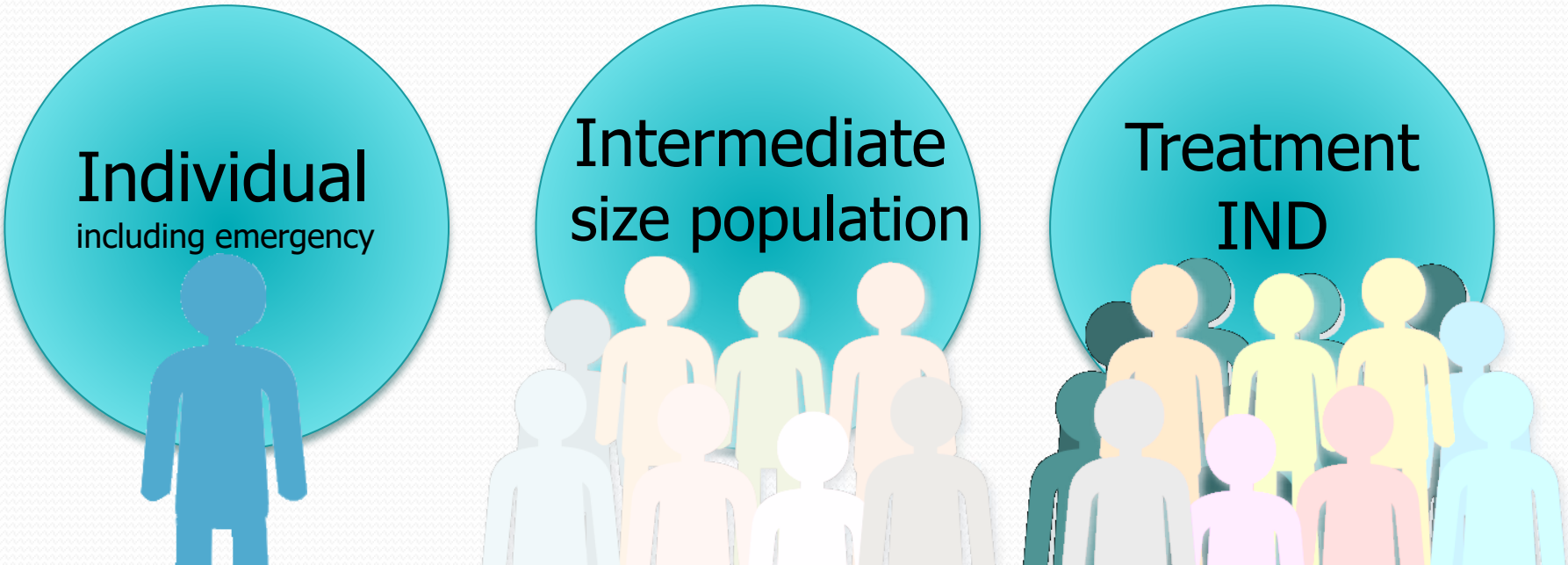
- Serious disease or condition: a disease or condition associated with morbidity having substantial impact on day-to-day functioning. Judged on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. (21 CFR 312.300)
- Immediately life-threatening disease or condition: a stage of disease with reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. (21 CFR 312.300)

Regulations 21 CFR 312 Subpart I

- Describe <u>two</u> categories of access, based on urgency:
  - **Emergency**: a situation that requires a patient to be treated before a written submission can be made – acute need, such as stroke or heart attack
    - Can be submitted electronically (email, phone, fax)
    - Paperwork must be submitted to FDA within 15 business days of authorization
    - Still requires informed consent, unless otherwise exempt (e.g., unconscious, cognitively impaired, no one else to provide consent
    - No prospective IRB review, report w/in 5 days
    - Applies only to a single patient
  - **Non-emergency**: all other patient access requests

Regulations 21 CFR 312 Subpart I

- Describe <u>three</u> distinct tiers of access based on size of group



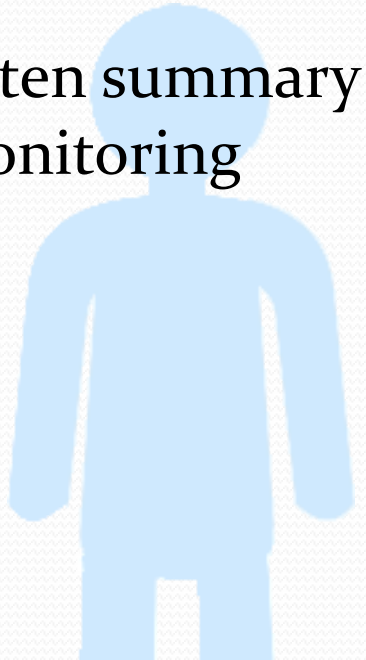
Individual Patient EAPs

21 CFR 312.310

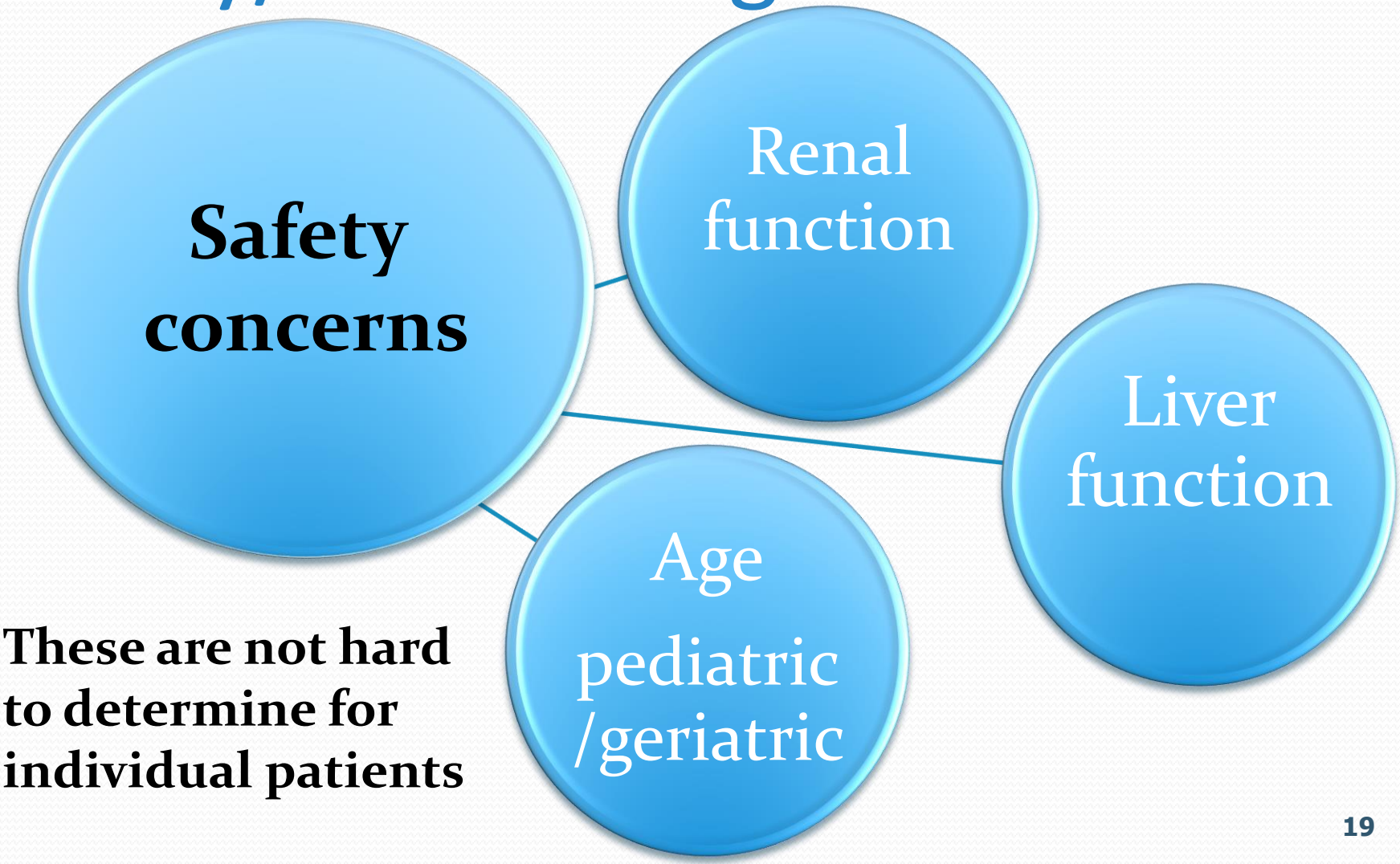
- Physician must determine probable risk from drug does not exceed that from disease
- FDA must determine that the patient cannot obtain access under another type of IND
- Regulations don't specify trail phase requirements
- Decisions based on benefit/risk determinations

Individual Patient EAPs

- Physician often takes role of sponsor/investigator (responsible for sponsor activities: IRB review, tracking, reporting etc.)
- Similar, but much less burdensome than clinical trail responsibilities
- FDA requires written summary report, and may require special monitoring



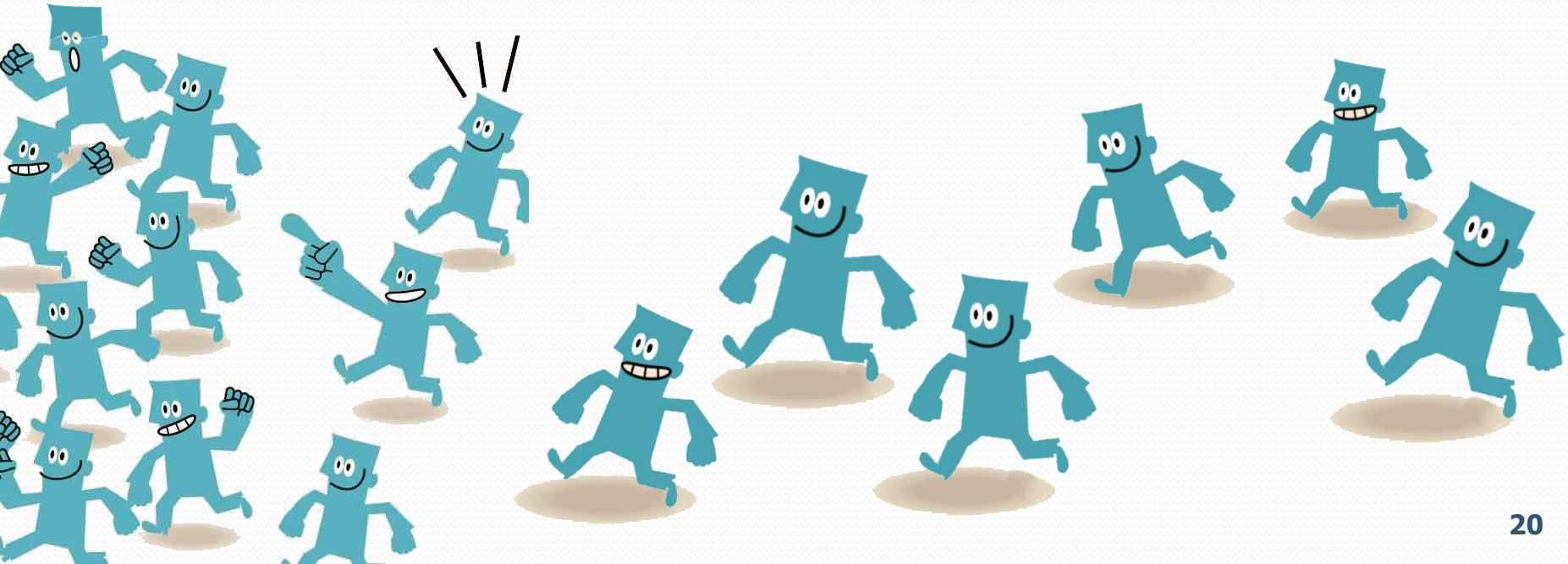
Safety/monitoring concerns



These are not hard to determine for individual patients

Safety in Numbers

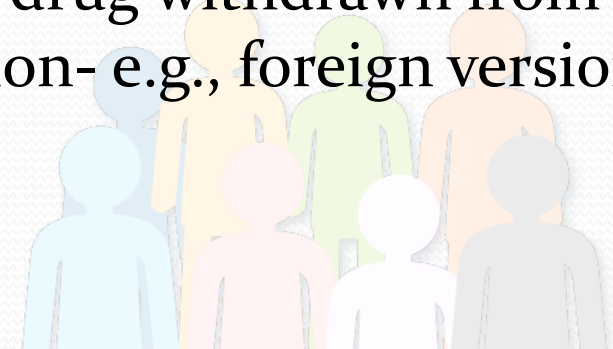
- There is a stepwise progression toward confidence in safety
- As data is accumulated, confidence rises, allowing broader access



Intermediate Size Population

21 CFR 312.315

- No fixed numerical requirement
- More than a few …less than a lot
- Is flexible: Can be used when a drug is
  - Being developed (e.g., patients not eligible for trial)
  - Not being developed (e.g., rare disease, cannot recruit for a trial)
  - Approved (e.g., drug withdrawn from market, drug shortage situation- e.g., foreign version of a U.S. approved drug)



Intermediate Size Population

- Sponsor can be physician, manufacturer, or 3rd party
- Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population
- Preliminary evidence (clinical, or plausible pharmacological) of effect
- Intended for patient populations smaller than intended for Treatment IND (generally up to 100 patients)
- Annual review to determine whether treatment use should be continued and whether a Treatment IND would be a more appropriate mechanism

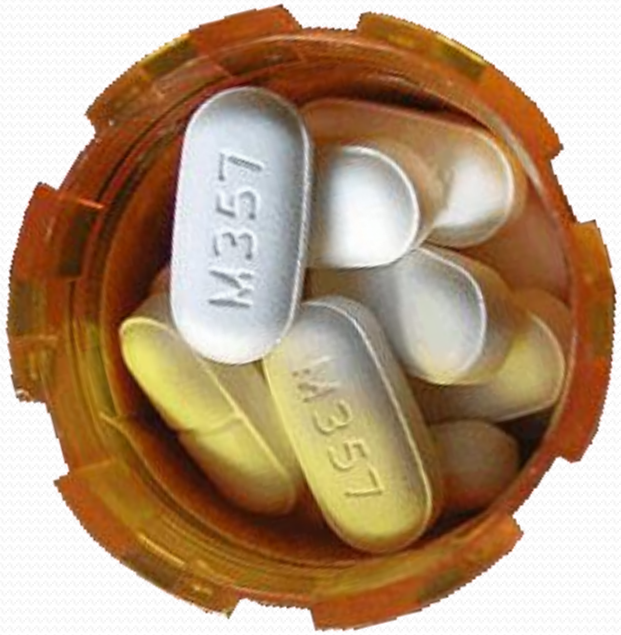
Treatment IND

21 CFR 321.320

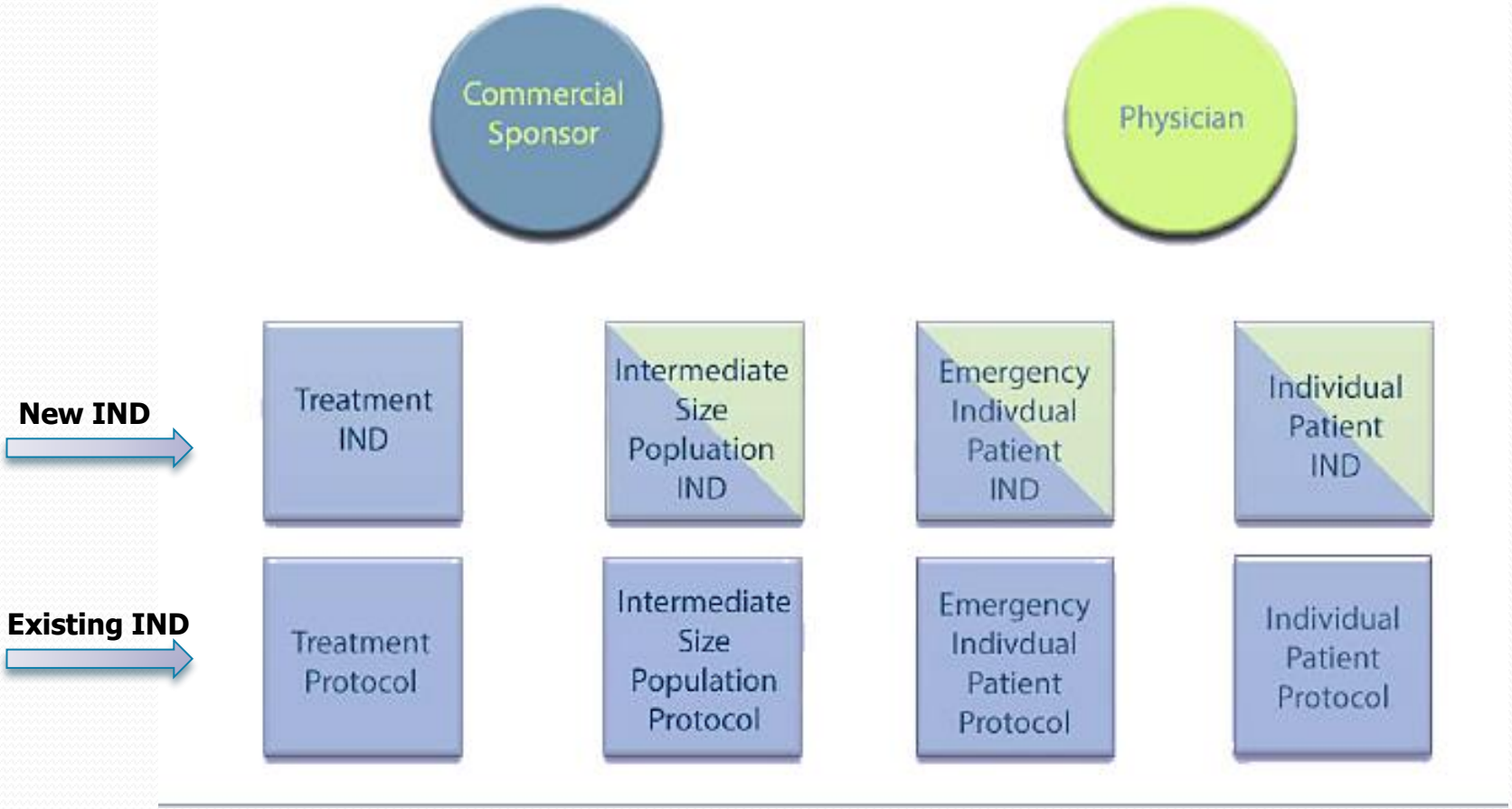
- Drug is being investigated in clinical trial designed to support marketing, or trials are complete
- Company is actively pursuing marketing approval
- Sufficient evidence of safety and effectiveness
  - Serious or life-threatening disease: evidence from phase 3 or compelling data from phase 2 clinical trials

Categories of Expanded Access

- In addition to "access INDs," access can be provided under an *existing* IND held by the manufacturer/sponsor of the research as an *access protocol*



Categories of Expanded Access



Human Subject Protections Apply to All EAPs

Drugs in EAPs are *investigational drugs*, so are subject to the following requirements from 21 CFR:

- Part 50 - Protection of Human Subjects (informed consent)
- Part 56 - Institutional Review Board (IRBs primarily responsible for review of Informed consent… Sole body with that responsibility)
- Part 312 - Reporting requirements (adverse event reports, annual reports), and *Clinical Holds* based on safety

Streamlining Access

FDA has been taking concrete steps to simplify the process for single patient access

- New, simplified application form – Form 3926
- Waiver of full-board IRB review, allowing concurrence by the IRB chair or designee (Can significantly reduce delays waiting for IRB review and approval)

What's the Application Process? *

- - After ensuring that the sponsor will provide the unapproved drug, the physician submits a written request to the appropriate FDA review division, consisting of:
- - Brief Clinical History of the patient including: diagnosis, status, prior therapy, rationale
- - Proposed Treatment Plan: dose, route, duration, monitoring procedures, modifications (e.g. dose reduction or treatment delay) for toxicity
- - Chemistry, Manufacturing, and Controls Information and Pharmacology and Toxicology Information, including a description of the manufacturing facility.
  ➡ Covered by Letter of Authorization (LOA) from sponsor 📎
- - Certification of IRB review and consent (except in emergency use)
- - Investigator Qualification Statement (Curriculum Vitae) 📎
- - Contact info of the IND sponsor

*Individual Patient IND

What's the Application Process?

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Individual Patient Expanded Access Investigational New Drug Application (IND)

(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0814
Expiration Date: April 30, 2019
See PRA Statement on last page.

1. Patient's Initials

2. Date of Submission *(mm/dd/yyyy)*

3.a. Initial Submission

☐ Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.

3.b. Follow-Up Submission

☐ Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.

Investigational Drug Name

Physician's IND Number

4. Clinical Information

Indication

Brief Clinical History *(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)*

5. Treatment Information

Investigational Drug Name

Name of the entity that will supply the drug *(generally the manufacturer)*

FDA Review Division *(if known)*

Treatment Plan *(Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)*

6. Letter of Authorization (LOA), if applicable *(generally obtained from the manufacturer of the drug)*

☐ I have attached the LOA. *(Attach the LOA; if electronic, use normal PDF functions for file attachments.)*

Note: If there is no LOA, consult the Form Instructions.

7. Physician's Qualification Statement *(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)*

8. Physician Name, Address, and Contact Information

Physician Name *(Sponsor)*	Email Address of Physician
Address 1 *(Street address, No P.O. boxes)*	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	Telephone Number of Physician
City / State	Facsimile (FAX) Number of Physician
ZIP Code	Physician's IND number, if known

PSC Publishing Services (301) 443-6740 EF

9. Contents of Submission

This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.

- ☐ Initial Written IND Safety Report
- ☐ Follow-up to a Written IND Safety Report
- ☐ Annual Report
- ☐ Summary of Expanded Access Use (treatment completed)
- ☐ Change in Treatment Plan
- ☐ General Correspondence
- ☐ Response to FDA Request for Information
- ☐ Response to Clinical Hold

10.a. Request for Authorization to Use Form FDA 3926

☐ I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

10.b. Request for Authorization to Use Alternative IRB Review Procedures

☐ I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

11. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, and that an Institutional Review Board (IRB) will be responsible for initial and continuing review and approval of this treatment use, consistent with applicable FDA requirements. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

Signature of Physician	**Date**
To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.	

For FDA Use Only

Date of FDA Receipt	Is this an emergency individual patient IND?	Is this indication for a rare disease (prevalence < 200,000 in the U.S.)?
IND Number	☐ Yes ☐ No	☐ Yes ☐ No

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 45 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

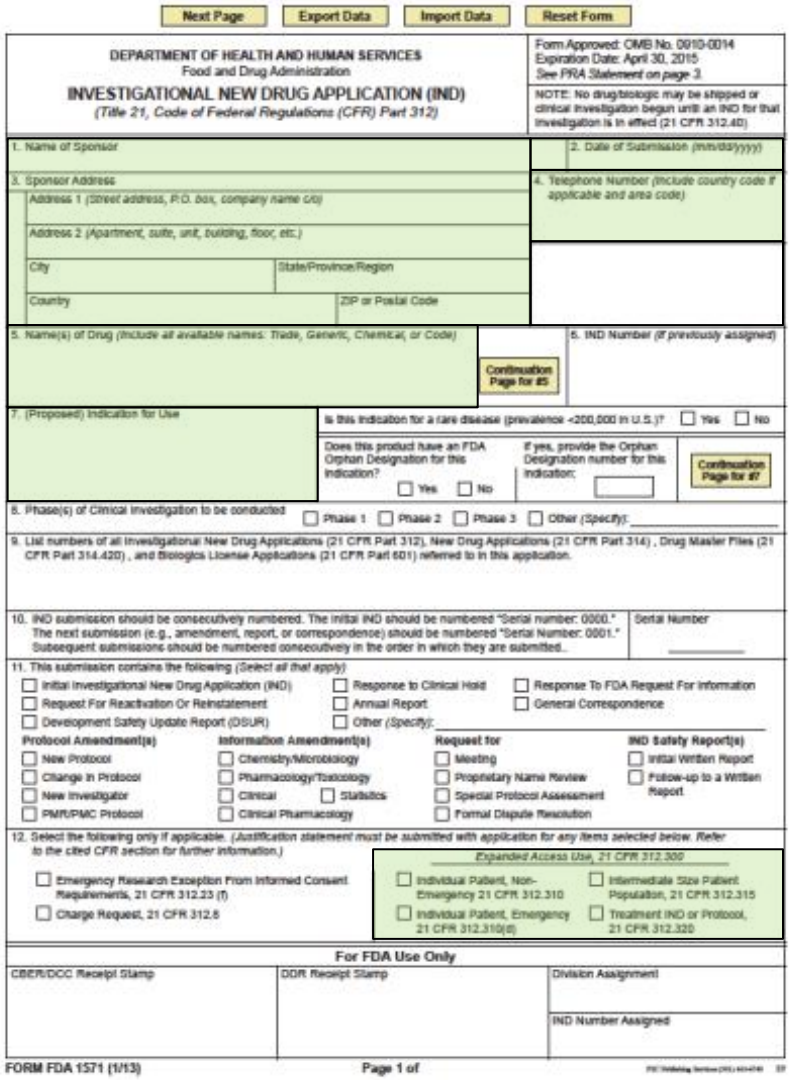
Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Takes about 45 minutes to complete

Form 1571

Typically intended for commercial IND applications



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

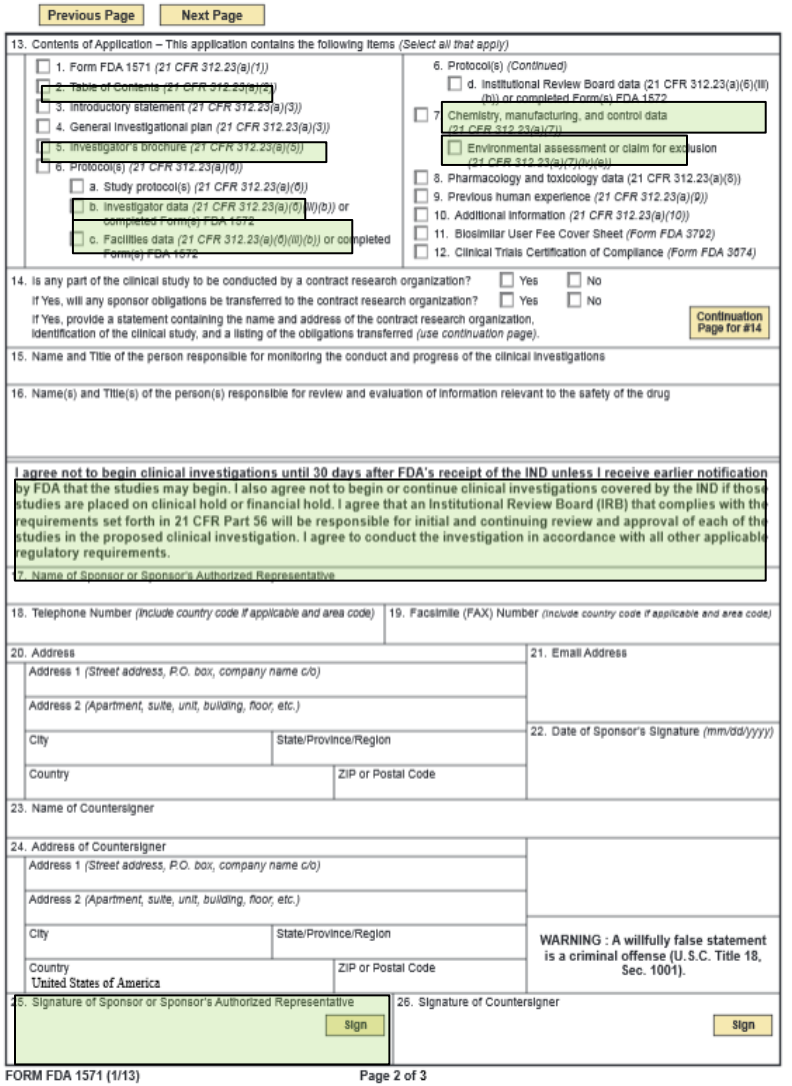
Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City | State/Province/Region
Country | ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (if previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No
Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other (Specify):
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.. Serial Number
11. This submission contains the following (Select all that apply)
☐ Initial Investigational New Drug Application (IND) ☐ Response to Clinical Hold ☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement ☐ Annual Report ☐ General Correspondence
☐ Development Safety Update Report (DSUR) ☐ Other (Specify):
Protocol Amendment(s): ☐ New Protocol ☐ Change in Protocol ☐ New Investigator ☐ PMR/PMC Protocol
Information Amendment(s): ☐ Chemistry/Microbiology ☐ Pharmacology/Toxicology ☐ Clinical ☐ Statistics ☐ Clinical Pharmacology
Request for: ☐ Meeting ☐ Proprietary Name Review ☐ Special Protocol Assessment ☐ Formal Dispute Resolution
IND Safety Report(s): ☐ Initial Written Report ☐ Follow-up to a Written Report
12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8
Expanded Access Use, 21 CFR 312.300
☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only
CBER/DCC Receipt Stamp | DDR Receipt Stamp | Division Assignment | IND Number Assigned

FORM FDA 1571 (1/13) Page 1 of



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13. Contents of Application – This application contains the following items (Select all that apply)
☐ 1. Form FDA 1571 (21 CFR 312.23(a)(1))
☐ 2. Table of Contents (21 CFR 312.23(a)(2))
☐ 3. Introductory statement (21 CFR 312.23(a)(3))
☐ 4. General investigational plan (21 CFR 312.23(a)(3))
☐ 5. Investigator's brochure (21 CFR 312.23(a)(5))
☐ 6. Protocol(s) (21 CFR 312.23(a)(6))
☐ a. Study protocol(s) (21 CFR 312.23(a)(6))
☐ b. Investigator data (21 CFR 312.23(a)(6)(ii)(b)) or completed Form(s) FDA 1572
☐ c. Facilities data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572
☐ 6. Protocol(s) (Continued)
☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572
☐ 7. Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7))
☐ Environmental assessment or claim for exclusion (21 CFR 312.23(a)(7)(iv)(e))
☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
☐ 9. Previous human experience (21 CFR 312.23(a)(9))
☐ 10. Additional information (21 CFR 312.23(a)(10))
☐ 11. Biosimilar User Fee Cover Sheet (Form FDA 3792)
☐ 12. Clinical Trials Certification of Compliance (Form FDA 3674)
14. Is any part of the clinical study to be conducted by a contract research organization? ☐ Yes ☐ No
If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☐ No
If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred (use continuation page).
Continuation Page for #14
15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations
16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug
I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.
17. Name of Sponsor or Sponsor's Authorized Representative
18. Telephone Number (Include country code if applicable and area code)
19. Facsimile (FAX) Number (Include country code if applicable and area code)
20. Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City | State/Province/Region
Country | ZIP or Postal Code
21. Email Address
22. Date of Sponsor's Signature (mm/dd/yyyy)
23. Name of Countersigner
24. Address of Countersigner
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City | State/Province/Region
Country: United States of America | ZIP or Postal Code
WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).
25. Signature of Sponsor or Sponsor's Authorized Representative — Sign
26. Signature of Countersigner — Sign

FORM FDA 1571 (1/13) Page 2 of 3

EAP-Implementing the process

A community responsibility

- The patient

Consults with their doctor to find and decide about alternative options

- The doctor

Works with manufacturer, files paperwork with FDA, IRB, and is responsible for patient care and reporting

- The industry sponsor

Provides the investigational product, and permits cross-reference to their original IND information

- FDA

Determines eligibility, judges the safety data, ensures patient protections are in place

- IRB

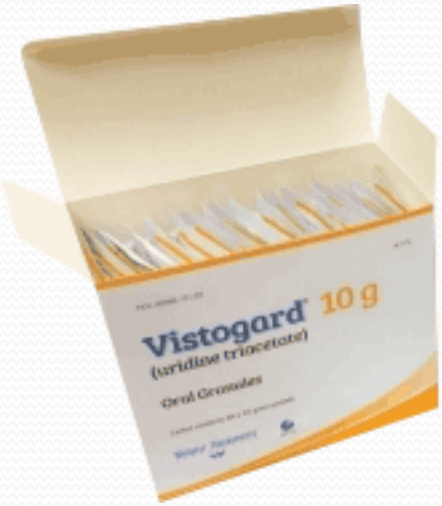
Reviews consent to assure patient is informed about investigational nature of treatment

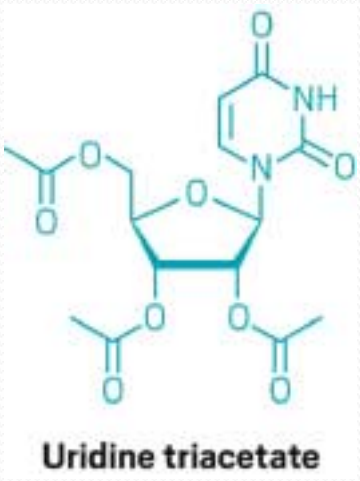
Does Expanded Access Support Approval?

- Not research subjects (technically…)
- Uncontrolled variables: organ function, overall health, disease stage, co-morbidities, concomitant drugs
- Intended to minimize data collection burden on physician
- Limited contribution to safety data
  - Reporting requirements for *serious and unexpected adverse reactions*

CAN Expanded Access Support Approval?

- Uridine triacetate: 2015
- Approved for chemotherapeutic overdose based solely on outcome of expanded access use





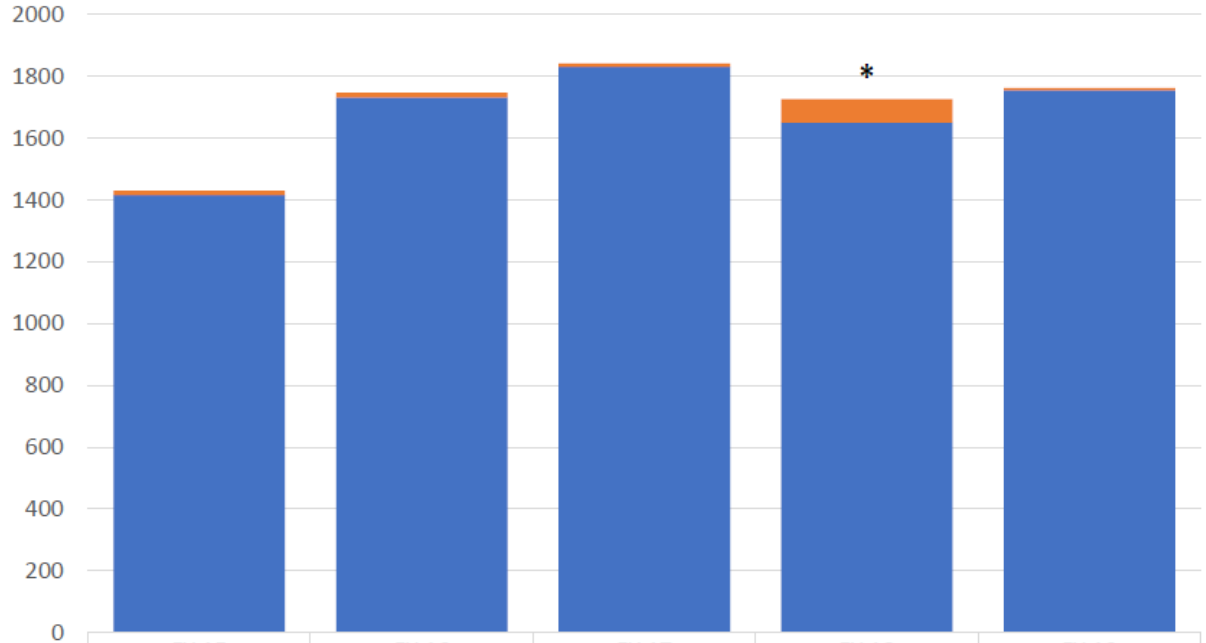
Uridine triacetate

Is FDA a Barrier to Access?

CBER* and CDER Expanded Access IND Submissions

Fiscal Year (FY) 2015 - 2019

**A large number of the FY18 single patient submissions were for non-emergency use of the same product, for which FDA determined the risks associated with its use would be unreasonable for the patients involved or there was insufficient information to make a determination. Excluding these submissions, 91% of CBER's non-emergency single patient expanded access submissions received were allowed to proceed.*

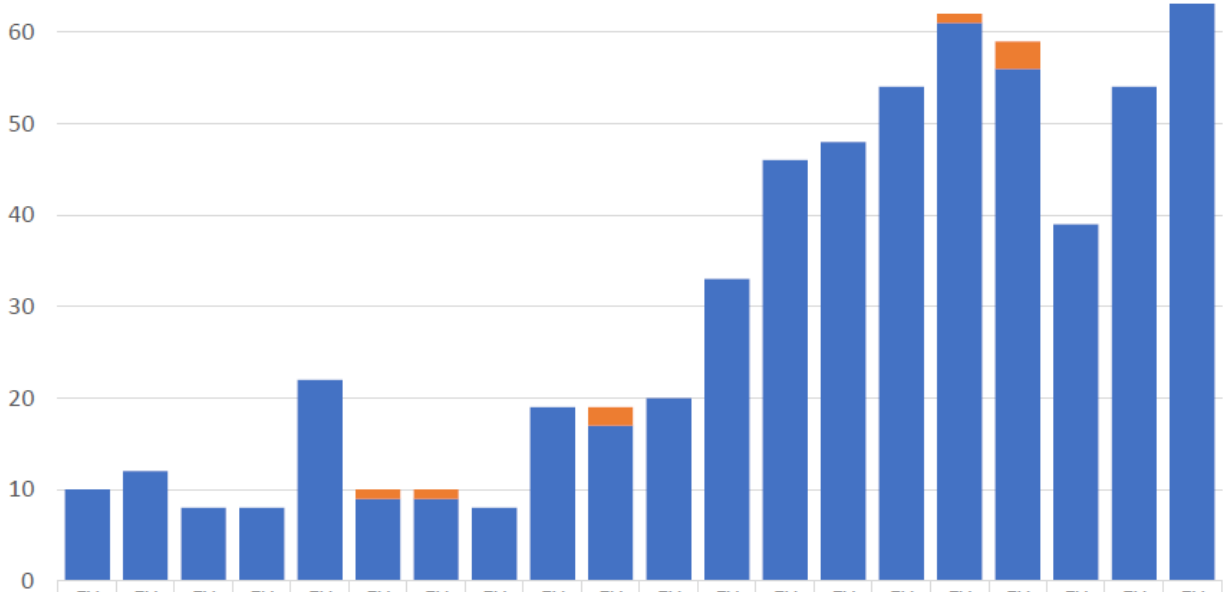


	FY 15	FY 16	FY 17	FY 18	FY 19
Not Allowed to Proceed	14	16	11	76	8
Allowed to Proceed	1416	1732	1831	1651	1755

Is FDA a Barrier to Access?

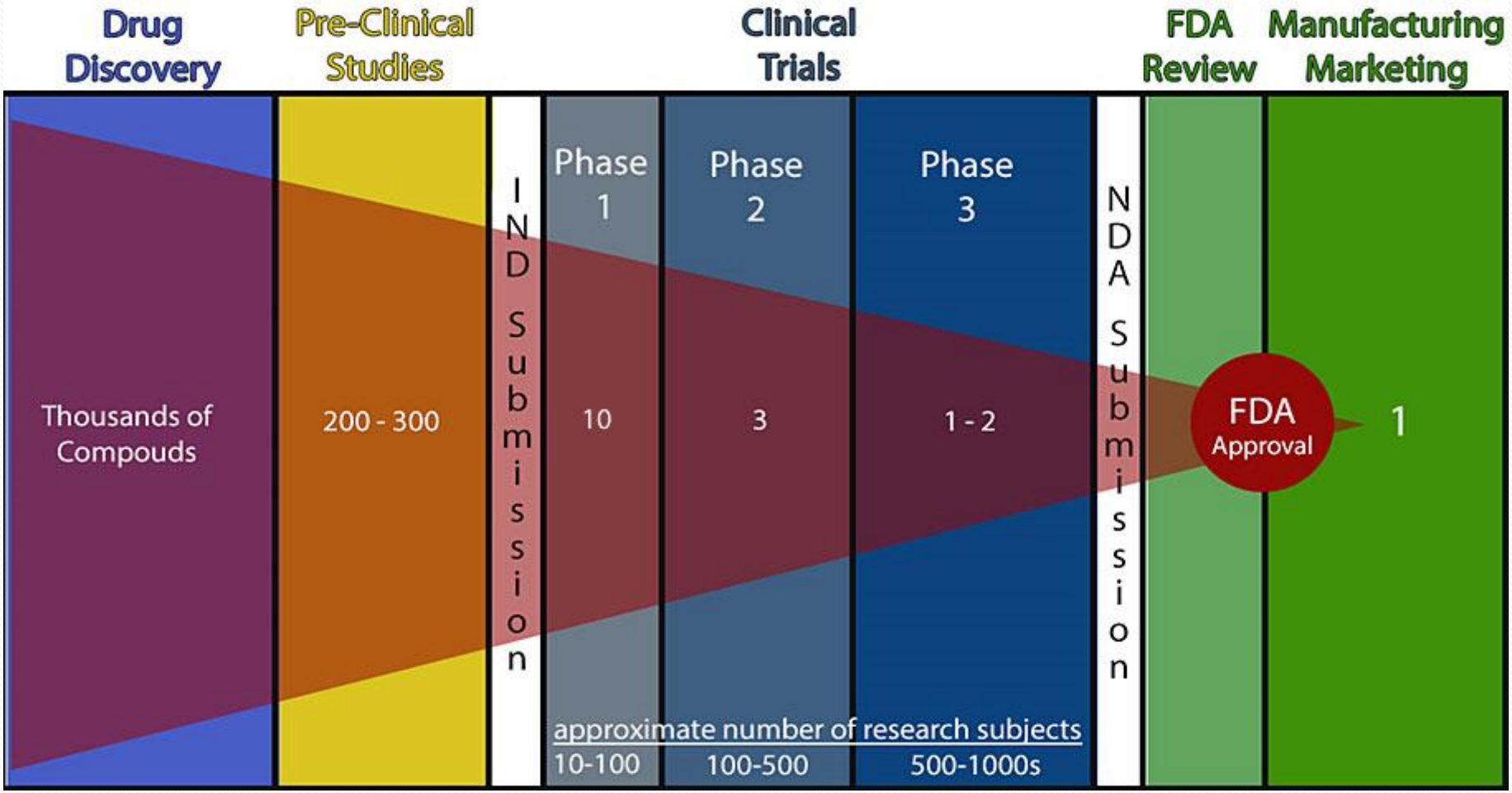
CBER and CDER Expanded Access Protocol Submissions

Fiscal Year (FY) 2015 - 2019



	Treatment Protocol					Intermediate Size Protocol					Individual (Single) Patient Emergency Protocol					Individual (Single) Patient Non-Emergency Protocol				
	FY 15	FY 16	FY 17	FY 18	FY 19	FY 15	FY 16	FY 17	FY 18	FY 19	FY 15	FY 16	FY 17	FY 18	FY 19	FY 15	FY 16	FY 17	FY 18	FY 19
Not Allowed to Proceed	0	0	0	0	0	1	1	0	0	2	0	0	0	0	0	1	3	0	0	0
Allowed To Proceed	10	12	8	8	22	9	9	8	19	17	20	33	46	48	54	61	56	39	54	80

Clinical Trials (Are drugs in development always good?)



Expanded Access Potential

Are investigational drugs safe?

- Filauridine (FIAU): investigated as a potential therapy for hepatitis B in 1993 @ NIH
  - Unexpected toxicity in phase 2 led to the death of 5 out of 15 patients from liver failure
  - Two further participants required liver transplants
  - Toxicity was not predicted by animal studies

- TGN1412, an immunomodulatory drug being studied for leukemia in 2006
  - Caused catastrophic systematic organ failure in phase 1 studies conducted by PAREXEL in London at doses 500 X lower than dose found safe in animal studies – 6 hospitalized

REUTERS

French drug trial disaster leaves one brain dead, five injured

2016

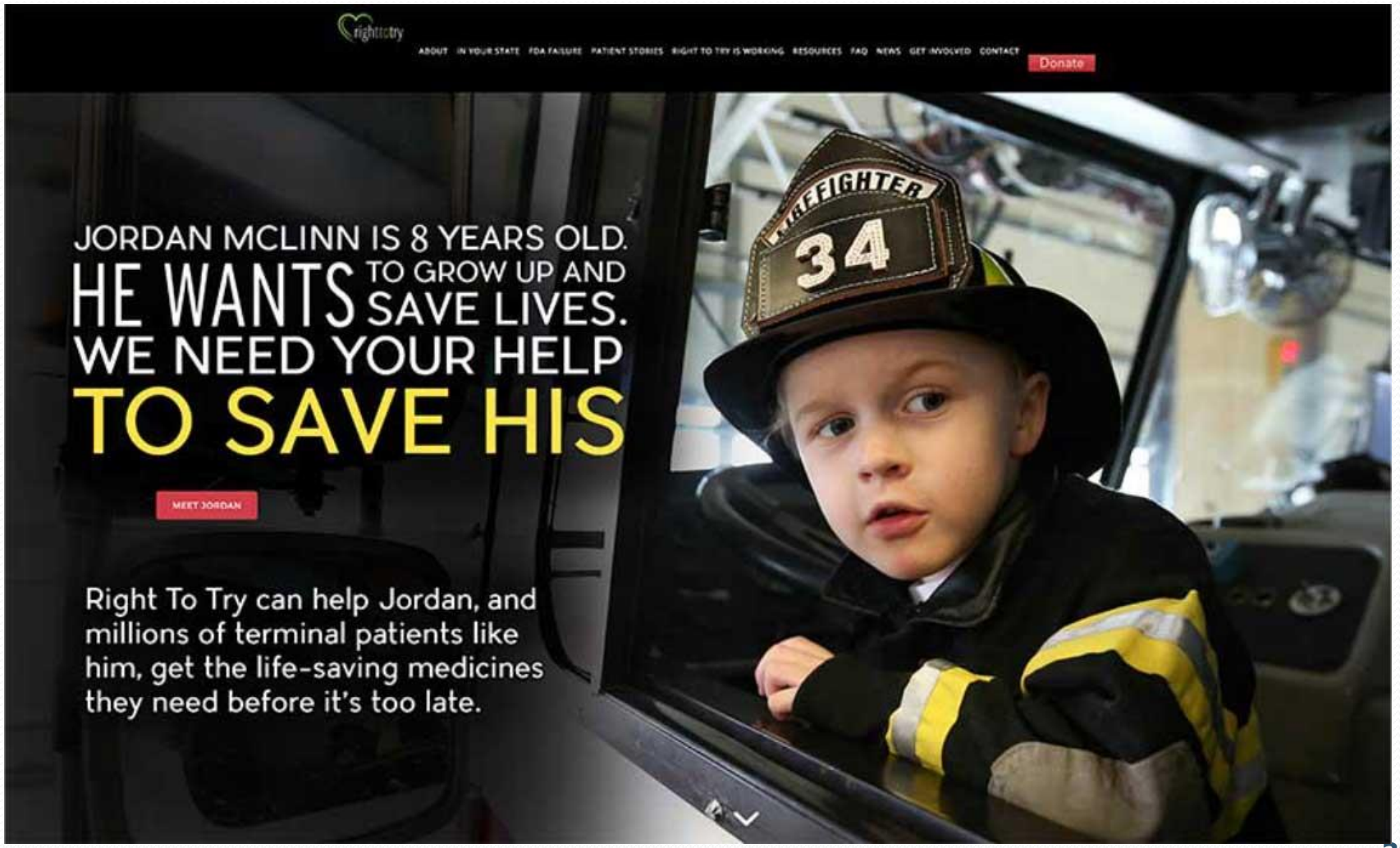
#WORLD NEWS JANUARY 15, 2016 / 5:41 AM / 2 YEARS AGO

French drug trial disaster leaves one brain dead, five injured

Matthias Blamont 4 MIN READ

PARIS - One person has been left brain dead and five others have been hospitalised after taking part in a clinical trial in France of an experimental drug made by Portuguese drug company Bial, French Health Minister Marisol Touraine said on Friday.

Right to Try campaigns state & federal



Right to Try

Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017

- An alternate pathway created by Congress to allow access by patients to investigational drugs in development post phase 1 study, without FDA involvement, for patients with life-threatening diseases or conditions who have exhausted approved therapy options, and cannot participate in a clinical trial

Right to Try

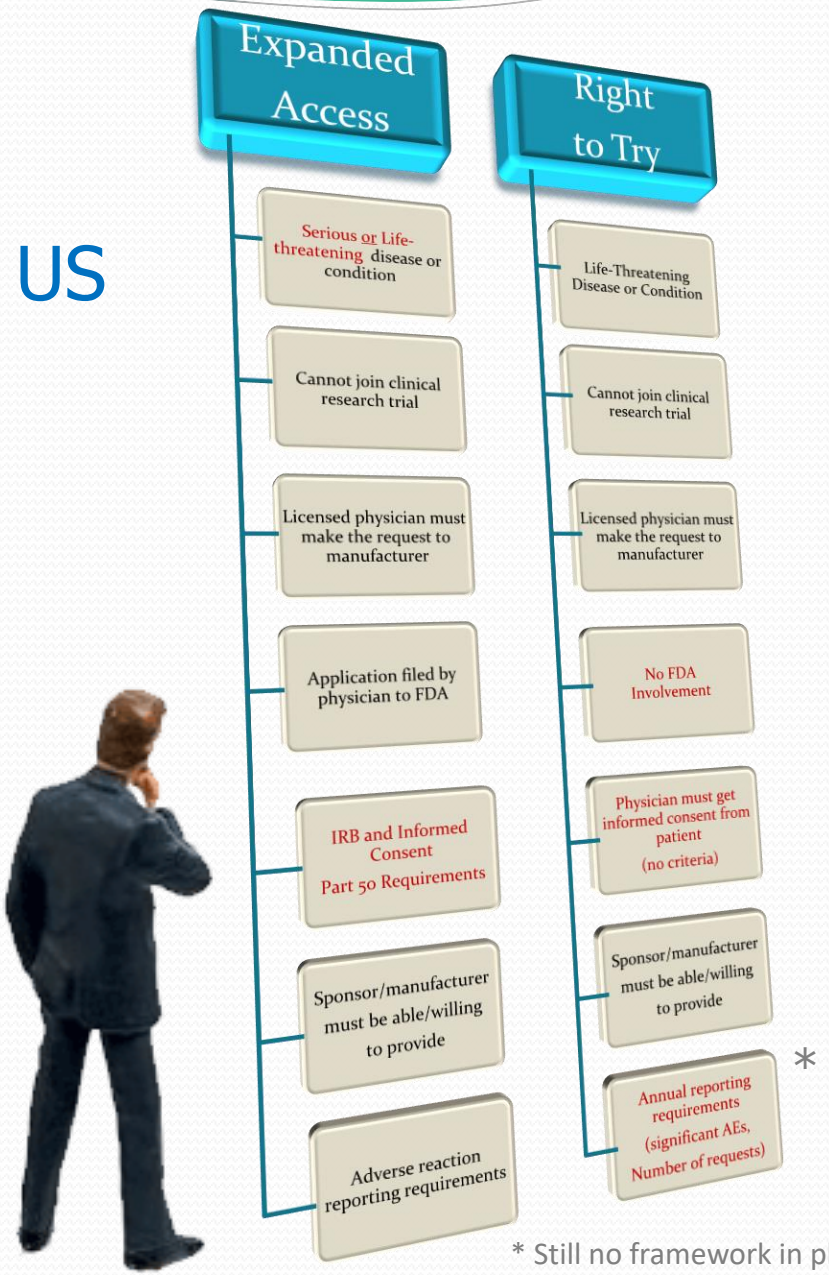
Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017

Signed into law 05/30/2018

- Applies solely to individual patients, not cohorts
- Investigational agent must have passed phase 1
- Must be in active development under an FDA IND
- Does not require the added protective oversight of IRB
- Requires informed consent, but does not dictate informed consent criteria (exempt from 21 CFR 50)
- Applies solely to drugs, not medical devices

Two pathways

Both can apply in US



* Still no framework in place

Other Challenges

- Big Company / Small Company
  - Different capacities
    - Personnel
    - Experience
    - Regulatory expertise, experience, and relationships
    - Global experience (laws, labeling, shipping)
  - Different financial profiles
    - Larger companies usually have the necessary resource (financial, expertise, personnel)

Corporate Challenges

- Financial capacity
- Supply (availability of drug)
- Medical/treatment resources
- Administrative burden, background costs
- Unpredictable demand
- Image/social media concerns
- Impact on investors
- Negative impact on clinical trials
- Legal and regulatory issues
- Managing access to limited resources *
  - Lottery? Sickest first? Age? First-come, first-served? Use of caps?

* Principles for allocation of scarce medical interventions
Govind Persad, Alan Wertheimer, Ezekiel J Emanuel
Lancet 2009; 373: 423–31

Managing Public Expectations

- Reasonable, or not…
  - Growing sense that patients have a right to investigational agents
  - Growing demand for access at all levels of development
  - Encouragement and increasing awareness from internet, and political influences

Global Policy Challenges

- Companies challenged by global variation in policies and pathways (e.g., EU has overarching regulations, but countries within have different policies, requirements, and procedures)
- Lack of a regulatory pathway in countries
- Access less is likely in countries where policies are unclear, difficult, or non-existent (Applying models from countries with successful programs to countries that don't have matured policies could improve global access)

Cost, and Cost Recovery

- Companies cannot make a profit on unapproved therapeutics
- Cost recovery in US limited to actual cost of manufacture
- Applies to both EA and RtT
- Physicians often not compensated for their time and efforts

Ethical Challenges

- Allocating scarce resources
  - Consistent application: like cases treated alike
  - Fairness
- Who makes decisions?
- Dispute Resolution/appeals: assure allocation principles appropriately applied, impartial review process
- Value of treatment -  - Quacks
- Threat to regulatory oversight and drug development(?)

Therapeutic Advances
present their own challenges

Cellular and gene therapy (Different set of challenges from small molecule therapies)

- Creating fair/ethical/practical programs
  - Sustainable long-term F/U
  - Consistent across portfolio
- Allocation of scarce resources
  - Limitation not only of product (e.g., vector production), beds, expertise
  - Complexity and cost of production
  - Complex storage and shipping challenges (biospecimens, temp control, etc.)
  - Special, certified facilities for treatment? (who pays?)
  - Travel necessity? Lodging? Family members? (who pays?)
    - Pediatric treatment of rare diseases requiring family accommodation

Real World Evidence

- Can contribute to effectiveness or safety data
- Might contribute to broader indication
- How will it be collected while avoiding added burden on physicians?

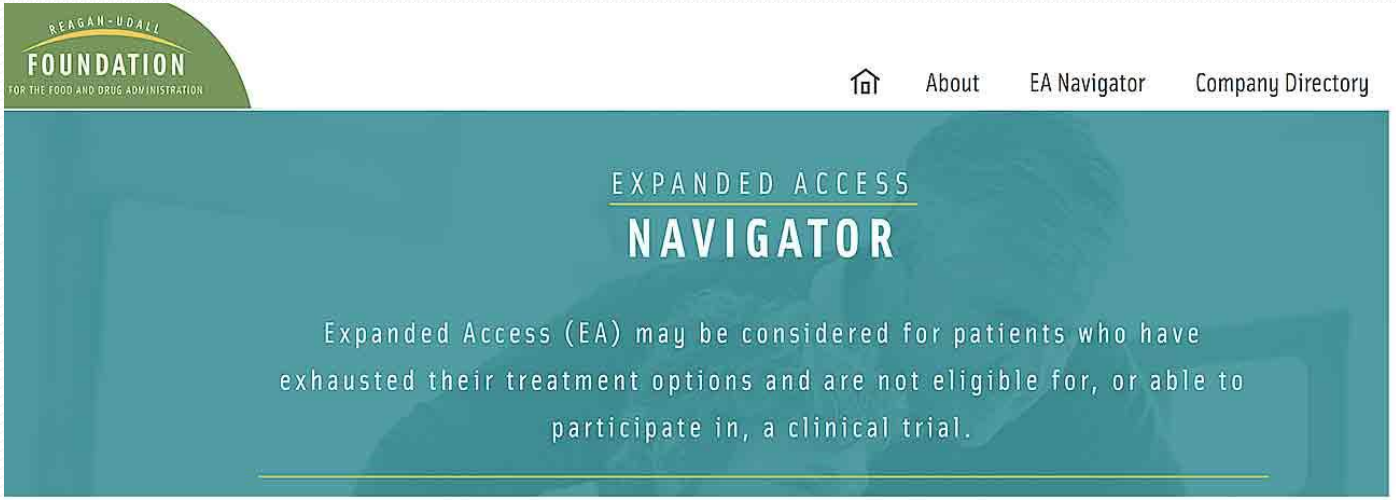
  (When does it become "research?")
- Patient Reported Outcomes?
  - What's collected and how?
  - Requires validated instruments

Exit Strategy

How to end a program

- When development ceases?
- Upon approval?
  - Not all countries approve at the same time
- Rights of patients already in treatment or in queue for access

Navigators


REAGAN-UDALL
FOUNDATION
FOR THE FOOD AND DRUG ADMINISTRATION
About
EA Navigator
Company Directory
EXPANDED ACCESS
NAVIGATOR
Expanded Access (EA) may be considered for patients who have exhausted their treatment options and are not eligible for, or able to participate in, a clinical trial.


KIDS V CANCER
Changing the landscape of pediatric research
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OUR IMPACT
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COMPASSIONATE USE NAVIGATOR
REQUEST OUR HELP
INFORMATION FOR FAMILIES
APPLICATION STEPS
Compassionate Use Navigator
Compassionate use is a pathway for very sick patients to try new, promising drugs that have not yet been approved. The Compassionate Use Navigator provides personal assistance and serves as a clearinghouse of up-to-date information on the compassionate use application process.

Emergency Use Authorization

- Medical countermeasures (MCMs) may be needed to prevent or treat diseases or conditions caused by chemical, biological, radiological, or nuclear (CBRN) or emerging infectious disease threats, like pandemic influenza or Covid-19
- Allows unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives
- Requires a declaration of a public health emergency
- Based on available data suggesting safety and efficacy

Additional Resources

For questions about FDA's expanded access program, contact the CDER Division of Drug Information at 855-543-3784 or druginfo@fda.hhs.gov

- FDA policies/procedures posted at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm
- Publicly accessible clinical trial and EAP Information: www.ClinicalTrials.gov
- Reagan-Udall Expanded Access Navigator http://navigator.reaganudall.org/
- NYU Working Group on Compassionate Use and Pre-Approval Access - https://med.nyu.edu/pophealth/divisions/medical-ethics/compassionate-use
- FDA Project Facilitate – a pilot program to assist oncology healthcare providers or regulatory professionals in requesting access to investigational therapies for patients with cancer https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate

KEEP CALM