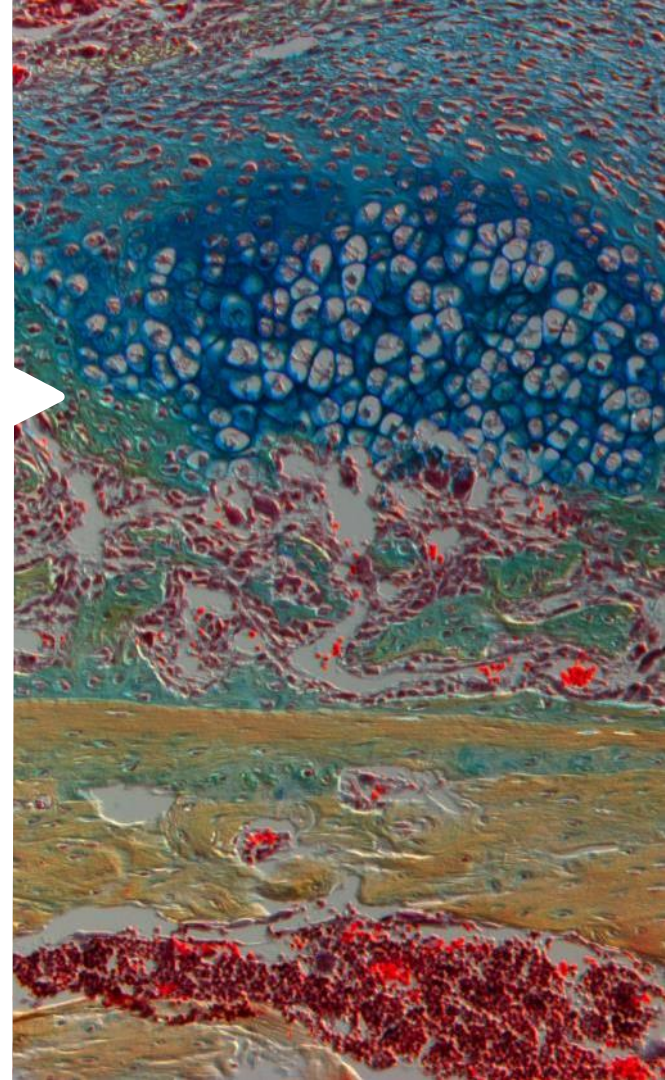




# Compassionate Use: The Ethics and Logistics of Using Investigational Medical Products outside of Clinical Trials

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## Disclosure

I serve as the non-voting, unpaid chair of several Compassionate Use Advisory Committees (CompACs), external, expert panels of internationally recognized medical experts, bioethicists, and patient representatives formed by NYU Langone Health to advise the Janssen division of Johnson & Johnson about requests for use of its investigational medicines.

I am a fellow of GE2P2, and, in that capacity, advise other pharmaceutical and biotech companies about pre-approval access.

I advise (pro bono) many patient advocacy groups about pre-approval access.

# Best way to get access to investigational drugs (and other treatments): clinical trial

- \* Rigorous investigation creates knowledge to help all
- \* Study team keeps a close eye on patients (benefit)
- \* Depending on study, participants may be provided the investigational drug after the study ends (“post-trial access”)

# **BUT...not all patients can participate in clinical trials**

\* limited slots

\* patient make not fit enrollment criteria (due to co-morbidities, past medical history, pregnancy, etc.)

\*geographic/financial/social barriers



**Some may not WANT to participate in a clinical trial**

# For patients who can't enter a clinical trial, several ways to try “experimental” products

- \* self-experimentation
- \* use approved products in a new way or for a condition other than what the drug was approved to treat (“off-label” use)
- \* personal importation from another country
- \* pre-approval access

# What is pre-approval access? Access to a medical product before it is approved by a regulator AND outside of a clinical trial

- \* Also known as “compassionate use”
- \* In the US, legal term is “**expanded access**” – under FDA oversight (Code of Federal Regulations, Title 21, Chapter 1, Subchapter D, Part 312)
- \* In the US, currently an effort to create way to access investigational drugs without FDA oversight (“Right to Try”)

## Outside of the U.S., terms used include:

“named patient programs”

“named patient supply”

“managed access”

“special access”

(and many others)

# Expanded Access

\* no comparable or satisfactory alternative therapy to **diagnose**, **monitor**, or **treat** the patient's disease or condition

\* 2 groups eligible for expanded access:

(1) those with life-threatening diseases/conditions for whom “there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without treatment” &

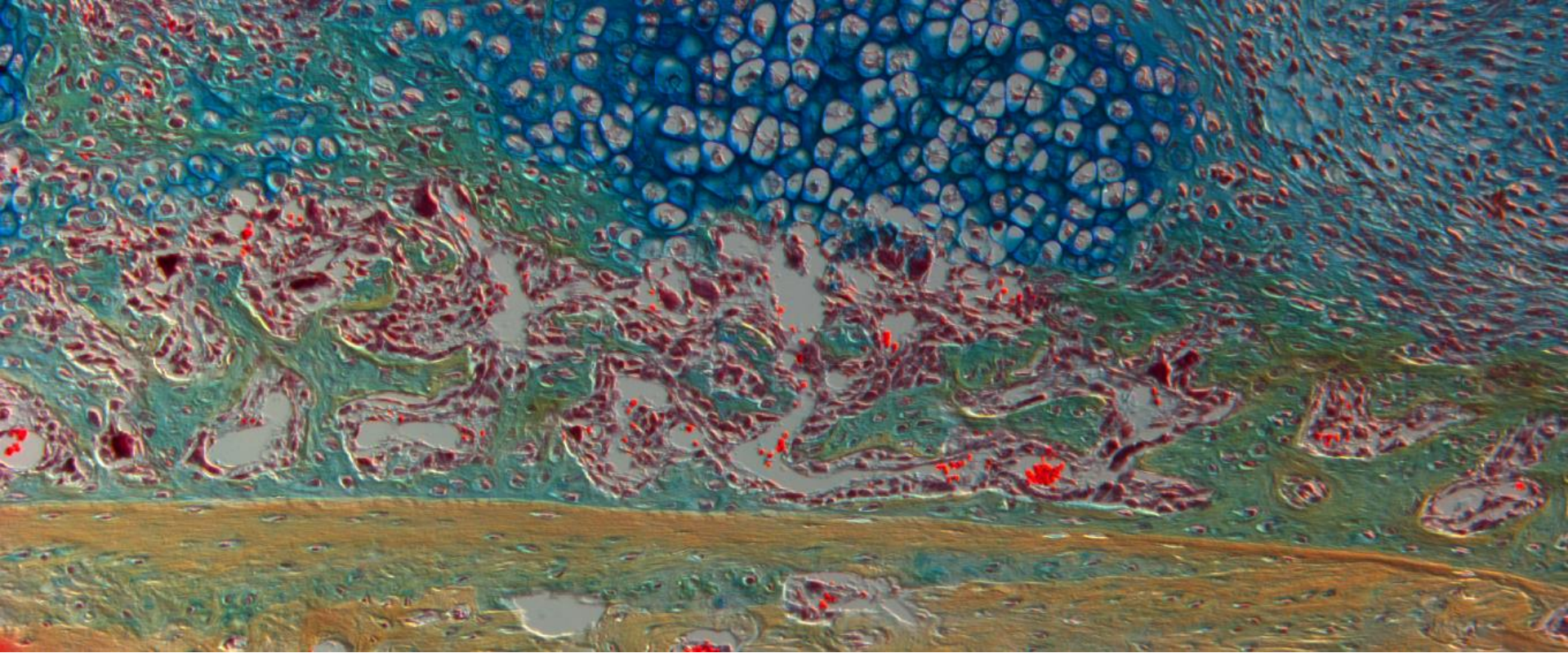
(2) those with serious diseases/conditions associated with “morbidity that has a substantial impact on day-to-day functioning”



 use of an investigational medical product to try to **treat** (aka, not for research, though data may be collected)

## Several different types of Expanded Access:

- \* emergency versus non-emergency
- \* individual patient EA / intermediate group EA / large group EA
- \* pure treatment vs treatment with data collection



## Recent Changes in U.S.

## Evolution over time

- Expanded access has existed since the 1970s.
- Became more widely used & known about during the 1980s (AIDS) & 1990s (breast cancer)
- In the 1990s, FDA revised the expanded access regulations
- Since the 1990s, there have been failed legislative efforts to change the system [undercurrent: “get the gov’t out of access to investigational drugs for very sick/dying patients”]

## The process:

- Identify willing physician / Identify promising drug
- Identify how to contact company
- Physician contacts company to request drug
- Physician contacts FDA to complete a form (w/ company's help)
- FDA reviews form, allows proposal to proceed or not
- Physician seeks IRB approval at institution where drug will be used
- Report serious/unexpected adverse events to FDA (and, as required, data to the company)

## “Right to Try” (*law in 38 states*)

- Identify willing physician / Identify promising drug
- Identify how to contact company
- Physician contacts company to request drug
- ~~Physician contacts FDA to complete a form (w/ company’s help)~~
- ~~FDA reviews form, allows proposal to proceed or not~~
- Physician seeks IRB approval at institution where drug will be used ??
- Report ~~serious/unexpected adverse events to FDA~~ (and, as required, data to the company)

## “Right to Try”

- Currently law in 38 states (though of questionable constitutionality)
- Federal RTT bill passed by Senate (in order to permit necessary FDA User Fee vote); now in House – failed last week, will return next week
- Unknown what the final provisions of the bill would be
- Unknown whether will need to go back to the Senate again
- Apparently only been used by 2 doctors in Texas
- Opposed by many patient groups (supported by some); opposed by ASCO & ACRO & me

## Why do I oppose RTT?

- FDA not obstacle (merely looks for biological plausibility of idea & known safety risks more severe than the patient's condition)



**Table 1: Total Expanded Access Requests Reviewed and Allowed to Proceed by Food and Drug Administration's (FDA) Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, by Type, Fiscal Years 2012 through 2015**

Type of request		Number reviewed	Allowed to proceed	Percent allowed to proceed
Single-patient	Emergency	2,451	2,436	99.4
	Non-emergency	3,047	3,016	99.0
Multiple patients	Intermediate-size	204	194	95.1
	Treatment (widespread)	51	51	100.0
<b>Total</b>		<b>5,753</b>	<b>5,697</b>	<b>99.0</b>



## Why do I oppose RTT?

- FDA not obstacle (merely looks for biological plausibility of idea & known safety risks more severe than the patient's condition)
- Companies unlikely to provide product without FDA sign-off
- FDA review is useful
- Removes monetary caps on what companies can charge patients ?
- Opens door to bad actors
- Multiple state RTT laws have bad provisions

## Patient-Hostile Provisions in Some State RTT laws

Patients may lose hospice coverage	AL, CA, CO, CT, FL, GA, ID, MI, MS, MT, NC, ND, SC, SD, TN, WV
Patients may be denied home health care coverage	CA, CO, CT, ND, OK, WV
Patients may lose health insurance; coverage can be denied for 6 mo after treatment ends	CO, CT, OK, WV
Insurers can deny coverage for treatment of harm caused by investigational product	UT

## Why do I oppose RTT?

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- Companies unlikely to provide product without FDA sign-off
- FDA review is useful
- Removes monetary caps on what companies can charge patients ?
- Opens door to bad actors
- Multiple state RTT laws have bad provisions
- Federal law has provision blocking FDA from **routinely** learning of bad outcomes (public health & consumer protection issue)

# So, is the current system perfect? NO!

## List of common concerns:

- Lack of knowledge = unequal access
- Concern about paperwork burden
- Fear about litigation
- Fear that a death would cause problems for development/approval
- Ancillary costs not covered by insurance
- Anecdotally, IRB review might cause problems (time, money)
- Fear that expanded access will hurt trials
- Fear that patients are unable to make a truly free & informed decision to try an investigational product
- Within FDA, divisions vary on receptivity to expanded access

# Myths

- Lack of knowledge = unequal access
- **Concern about paperwork burden**
- **Fear about litigation**
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## FDA has taken action... (even though this was a myth)

- Concern about paperwork burden
  - Introduced streamlined form for single patient requests
  - Released updated guidance documents
  - Has dedicated staff you can call for help

## Other FDA actions...

- Lack of knowledge = unequal access
- ~~Concern about paperwork burden~~
- ~~Fear about litigation~~
- ~~Fear that a death would cause problems for development/approval~~
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## Other FDA/gov't actions...

- **Lack of knowledge = unequal access**
  - FDA charged the Reagan Udall Foundation of the FDA to create an “Expanded Access Navigator” website
  - ClinicalTrials.gov revised to make it possibly to more easily search for expanded access opportunities
  - 21<sup>st</sup> Century Cures bill (passed Dec 2016) mandates companies to provide their expanded access policy to the public when any of the products move to Phase II testing
  - FDA released updated guidance documents
  - FDA revised their webpage dealing with expanded access



## Other FDA/gov't actions...

- IRB review might cause problems (time, money)
  - October 2017, FDA updated guideline for FDA review of expanded access – intended to make it faster

- ~~• Lack of knowledge = unequal access\*~~
- ~~• Concern about paperwork burden~~
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- **Fear that expanded access will hurt trials**
  - FDA restricts expanded access to those who have “no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition”
  - Companies must restrict expanded access to those who are ineligible for their trials (physically, geographically, socially). Mere unwillingness to participate in a trial should not suffice.
  - That said, companies should try to make the trials as appealing as possible (with regard to study design, procedures, etc.)

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials; Public Meeting

A Notice by the [Food and Drug Administration](#) on 01/30/2018



## PUBLISHED DOCUMENT



### AGENCY:

Food and Drug Administration, HHS.



### ACTION:

Notice of public meeting.



### SUMMARY:

The Food and Drug Administration (FDA, the Agency, or we) is announcing a public meeting entitled “Evaluating Inclusion and Exclusion Criteria in Clinical Trials.” Convened by the Duke-Robert J. Margolis, MD, Center for Health Policy



## DOCUMENT DETAILS

### Printed version:

[PDF](#)

### Publication Date:

01/30/2018

### Agencies:

[Food and Drug Administration](#)

### Dates:

The public meeting will be held on April 16, 2018, from 8:30 a.m. to 5 p.m. See the SUPPLEMENTARY INFORMATION section for registration date and information.

- ~~• Lack of knowledge = unequal access\*~~
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- **Fear that patients are unable to make a truly free & informed decision to try an investigational product**
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- Fear that patients are unable to make a truly free & informed decision to try an investigational product
  - If true, no (ethical) clinical trials!
  - Capacity for free and informed decision-making must be individually assessed, but there is no ethical reason to assume that patients who have no other options are incapable of making treatment or research decisions.

- ~~• Lack of knowledge = unequal access\*~~
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- **Within FDA, divisions vary on receptivity to expanded access**

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- ???????
- If so, is a problem that FDA administration must fix
- (FDA can only approve what it gets, so if there is less expanded access in Neurology than in other divisions, it may be that neurologists submit less requests than, say, their peers in oncology and/or that drug companies are declining to provide product)



**Table 2: Number of Expanded Access Requests Reviewed by Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER), by Division and Type of Request, Fiscal Years 2012 through 2015**


Division	Single-patient		Multiple patients		Total	Percent
	Emergency	Non-emergency	Intermediate-size	Treatment (widespread)		
Anti-infective	261	1,031	4	0	<b>1,296</b>	25.6
Antiviral	911	70	2	0	<b>983</b>	19.4
Hematology	466	406	12	8	<b>892</b>	17.6
Oncology 2	20	521	14	15	<b>570</b>	11.3
Gastroenterology and Inborn Errors of Metabolism	291	124	52	2	<b>469</b>	9.3
Oncology 1	39	398	2	3	<b>442</b>	8.7
Neurology	60	88	58	2	<b>208</b>	4.1
All other divisions <sup>a</sup>	74	85	30	12	<b>201</b>	4.0
<b>Total</b>	<b>2,122</b>	<b>2,723</b>	<b>174</b>	<b>42</b>	<b>5,061</b>	<b>100.0</b>

Source: GAO analysis of FDA data. | GAO-17-564

- ~~• Lack of knowledge = unequal access\*~~
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- ~~• Anecdotally, IRB review might cause problems (time, money)\*~~
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- Ancillary costs not covered by insurance
  - Varies by insurer, but generally true – insurance does not pay for investigational therapies or ancillary costs incurred outside of clinical trials (including doctors' time)
  - Makes some doctors/institutions unwilling to participate in expanded access
  - Covering these costs may help with the unequal access issue

## Where we need to do more

- **Lack of knowledge = unequal access** 
- Concern about paperwork burden
- Fear about litigation
- Fear that a death would cause problems for development/approval
- **Ancillary costs not covered by insurance**
- **Anecdotally, IRB review might cause problems (time, money)**
- Fear that expanded access will hurt trials
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**Equally important - must work with companies to identify incentives/disincentives for them to make their products available re expanded access.**



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# Thank You

Check out FAQs & resources on the Working Group on  
Compassionate Use and Pre-Approval Access' webpage  
– search for “NYU Compassionate Use”

