Compassionate Use of Investigational Drugs:

Accessing Unapproved Therapies for Pediatric Oncology Patients

Elena Gerasimov, MA, MPH
Director, Compassionate Use Navigator Program
Kids v Cancer, Washington, D.C.

www.kidsvcancer.org

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Kids v Cancer Compassionate Use Navigator

• Created in April 2016. Inspired by the Josh Hardy case. Available at: http://www.kidsvcancer.org/compassionate-use/reports/.
• Assists physicians and families.
• Addresses informational barriers.

ONLY PHYSICIANS CAN REQUEST ACCESS TO COMPASSIONATE USE DRUGS
“The biggest learning for this audience was that it is NOT the FDA withholding applications for compassionate use.” Erin Benson, Speaker, DIPG Symposium, Cincinnati, May 5-6, 2017.

“The one thing I wish could have been different with the compassionate use program is that I would have known about it earlier.” Nicole Pierson, Life Science Leader, May 9, 2017.

“Certain groups – physicians with clinical research experience, their patients, and computer-savvy patients with time to research EAP drug availability – have a great advantage in gaining access to these limited programs. This is unfair.” Stuart L. Nightingale, MD. FDA Expanded Access Programs for Experimental Medicines. Letter to the Editor. JAMA. 2015; 314(12):1296.
Compassionate Use: Definition

• Compassionate use refers to the use of experimental/investigational drugs.

• It is intended for a patient with “immediately life-threatening condition or serious disease” who cannot wait for a therapy’s approval and for whom no comparable or satisfactory alternative therapies are available.

• The goal is treatment, not research, generally limited to a single course of therapy for a specified duration.

For providers: Consider compassionate use if your patient is refractory or has relapsed, has tried all known and studied therapies, and you have an idea about possible drug efficacy.
Compassionate Use: Definition (cont.)

• Compassionate use happens **outside of a clinical trial.**
  • Ex.: Patients cannot enroll into a trial because they are ineligible, cannot relocate in order to participate in a trial, a trial is not recruiting or has ended.

• For cancer patients compassionate use requests **may also include off-label usage** if insurers refuse to pay for the treatment. Ex:
  • Erdfatinib for a glioma patient;
  • Olaparib for neuroblastoma patient;
  • Osimertinib for EGFR mutated mNSCLC with leptomeningeal mets;
  • Palbociclib for osteosarcoma with CDK4 amplification;
  • Abemaciclib and trametinib for pilocytic astrocytoma.
Terminology: Single versus Multiple Patients Access

**IND** = Investigational New Drug, refers to an application to FDA

- **EAPs**: Multipatient cohort programs tend to have established eligibility criteria.
- Often used upon completion of a trial.
- Most are listed on Clinicaltrials.gov.
How do patients find compassionate use drugs?

• Through their physician;
• Internet, including ClinicalTrials.gov;
• Patient organizations, forums, word-of-mouth.

How do providers find compassionate use drugs?

• Knowledge of clinical trials;
• Learn from colleagues;
• Drug manufacturers’ websites;
• Other websites: PubMed, Drug Interaction Database
Application Overview for a Single Patient IND:
A 3-Step Process

1. Apply to a drug manufacturer.

2. Apply to the U.S. Food and Drug Administration.

3. Apply for IRB approval.
Step 1. Apply to Drug Manufacturers

• Contact the company: Look for the company’s Expanded Access page.

• Ask the company to provide the drug for your patient, via a website online form or by email. Explain your patient’s history, your choice of investigational drug, why a clinical trial is not an option.

• If a denial is not justified in your view, try again. You might want to find a colleague who has obtained the experimental drug you are seeking and use prior case evidence to support your request.

• If the company agrees to provide the drug, it will issue you a **Letter of Authorization**.
  -- Allows FDA to refer to information that the sponsor of the IND has submitted to FDA with certain necessary information about the investigational medical product (e.g., chemistry, manufacturing, controls).
  Ex.: [https://www.fda.gov/news-events/expanded-access/example-wording-letter-authorization-loa-individual-patient-expanded-access-ind](https://www.fda.gov/news-events/expanded-access/example-wording-letter-authorization-loa-individual-patient-expanded-access-ind)

**Timeframe:**

*Up to 1 hour to send an initial inquiry.*
*Response timeline varies, up to one week.*
*Issuance of a LoA may take weeks in non-emergency cases.*
Step 1. Drug Manufacturers: Examples of Policies

The most challenging step is obtaining agreement from a drug company to provide a drug.
- Companies are NOT required to provide drugs on compassionate use basis.
- They are required to have information on their website about the application process.
- **Do not get discouraged**! Even if the company states it does not provide expanded access, you should try.

“[…at this stage of the development of our products there is insufficient clinical data to support expanded access use and we are unable to manufacture our investigational drugs in the quantities that may be needed for expanded access purposes. Therefore, to ensure availability of materials for clinical trial research and the safety of potential patients, Frequency Therapeutics does not provide access to our investigational products through expanded access currently.”

“[In rare cases when patients with serious diseases are unable to participate in clinical trials and have exhausted all available therapies, WonderDrug may consider providing an investigational drug outside of a clinical trial. As a general policy, WonderDrug will not provide investigational drug until sufficient preliminary safety and efficacy information has been obtained in clinical trials, typically following Phase 2 investigation.”
Step 2. Apply to FDA

FDA authorizes over 99% of expanded access requests.

- Complete Form 3926. Form and instructions: [https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians](https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians).
- Enclose LoA from the drug company.
- Contact FDA Review Division for drugs, biologics, or devices, or Project Facilitate with questions. Contact information for FDA review divisions can be found on FDA’s website: [https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information](https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information).

**Timeframe:**

*Response timeline:*
- *same day for emergencies, 2-3 days for non-emergent oncology requests.*

Enlist staff to help (CRA, PA, RN, NP, MPH) to fill out and submit FDA’s Form 3926.

You will need:
- Name of the drug;
- Clinical history of your patient;
- FDA Review Division mailing address.
FDA Project Facilitate

- Single point of contact, pilot program: Oncology Center of Excellence call center to assist healthcare providers in requesting access to investigational therapies for patients with cancer.

**Contact:**

- **Healthcare providers:** call Project Facilitate at (240) 402-0004 from 8 a.m. to 4:30 p.m. ET, M-F. **For emergency requests,** after 4:30 p.m. ET weekdays and all day on weekends: contact FDA's Emergency Call Center at 866-300-4374.

- Submit oncology expanded access requests via email at: [OncProjectFacilitate@fda.hhs.gov](mailto:OncProjectFacilitate@fda.hhs.gov).

Website: [https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate](https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate).

**For Patients and Families**

For questions, please call FDA’s Division of Drug Information at 301-796-3400 or email [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).
Step 2. FDA Mailing Addresses

**Individual Patient Expanded Access Investigational Drugs:**
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
ATTN: [appropriate Review Division]
“EXPANDED ACCESS SUBMISSION”
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

**Investigational Biologics:**
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002

For non-emergent requests, you can file electronically via E-Request:
https://erequest.navigator.reaganudall.org/#/home/landing
Step 3. IRB Review and Informed Consent

• **Obtain informed consent** before contacting IRB or proceeding with treatment.
  -- Sample informed consent from University of Michigan: https://az.research.umich.edu/medschool/templates/fda-expanded-access-informed-consent-template
• In an emergency, report compassionate use to the IRB within 5 days of treatment initiation.
• In non-emergency, a sign-off by the chair or another member of the IRB is required. Full IRB committee meeting is no longer necessary.

**If your institution does not have an IRB:**
  -- Contact an independent IRB familiar with reviewing compassionate use requests, ex: Quorum Review IRB, Advarra, Sterling IRB.

**Timeframe:**

*Up to an hour for informed consent.*
*Up to an hour to locate and meet with an IRB representative.*
*Enlist staff to help (CRA, PA, NP, RN, MPH).*
Emergency Applications

• **Urgent need for treatment** – no time to waste.
  - Call FDA. FDA usually grants emergency use requests for an individual oncology patient verbally the same day. Non-emergency requests are generally reviewed within a few days.
  - Certain paperwork, such as Form 3926 and the letter of authorization, can be submitted to FDA within 15 days of treatment initiation.
  - When there is not sufficient time to secure IRB review prior to treatment, the IRB must be notified within 5 working days of emergency use.
  - Informed consent must be obtained prior to treatment.

For emergency requests for all medical products (drugs, biologics, and medical devices) contact FDA's Emergency Call Center at 866-300-4374.
Family Expectations for Compassionate Use

- Requests can only be submitted by a physician.
- Parents of a child with cancer are willing to do everything in their power to obtain access to a therapy they believe might save or prolong a child’s life.
- Families do their research and are often knowledgeable about drug development. There will be an expectation that their oncologist will pursue a compassionate use request.

The biggest hurdle in getting access to investigational drugs is obtaining agreement from manufacturers to provide the drug.
Physician Considerations for Compassionate use

• Identification of a promising investigational drug;
• Concerns about potential toxicities of investigational drugs => Need to balance uncertainty and risks of the disease itself;
• Lack of clinical evidence of effectiveness to justify investigational treatment for a specific indication;
• Safety concerns related to the condition of a patient.

The compassionate use application requires knowledge of the regulations and administrative process.

Compassionate use of investigational cancer drugs in children can be considered even if the drug has not been previously studied in children.
Assistance for Physicians and Families

Compassionate Use Navigator

• Questions answered
• Live assistance to guide physicians in every step of the process.
• Locate drug manufacturers’ contact information.
• Provide templates and helps draft an initial request to a drug manufacturer.
• Help with FDA Form 3926.
• Help locate an IRB.

Contact:
Elena Gerasimov, Program Director,
Ph. 202-271-2855 or Elena@kidsvcancer.org.
https://www.kidsvcancer.org/compassionate-use/
Assistance for Physicians

Reagan-Udall Foundation Expanded Access Navigator

- Provides physicians, patients, and caregivers with guidance on EA and related topics.
- Explains the application process, including clinical trials.
- Directory of companies with expanded access program.
- Electronic submission for non-emergency requests to FDA.
- Has links to IRBs databases.

Contact:
Phone: (202) 849 - 2075
https://navigator.reaganudall.org/expanded-access-navigator
Right to Try

RTT is a federal law passed in 2018. Another attempt for patients to access certain unapproved treatments. Unlike a single patient IND:

- Eligible drugs must have **completed Phase 1** trial.
- FDA **does not review or approve** requests for Right to Try Act use.
- Individual Right to Try Act requests **do not require IRB review** or approval.
- Request can be submitted by physician or **patient**.

**Why not to consider this strategy:**

- RTT does not require a drug sponsor to provide the investigational product => “Right to Ask”.
- Does not include an evaluation of the safety and overall benefit/risk assessment by a third party (FDA and IRB).
- In practice has lower success chance because companies are more likely to want to involve FDA => the number of successful RTT requests is not known.
Thank you!

• Visit our website: Kidsv cancancer.org
• Email: Elena@kidsv cancancer.org