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Use of “Supplemental” Data: Expanded Access Programs

Meeting 3, Committee on Processes to Evaluate the Safety & Efficacy of Drugs for Rare Diseases in the US and the EU

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Disclosures

Bateman-House has written and spoken about the use of Expanded Access as a source of supplementary data for many audiences including the Reagan-Udall Foundation for the FDA; she received an honorarium for doing so for PRIM&R (Public Responsibility in Medicine and Research).

What is Expanded Access?

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How do people access medical products before regulatory approval?

- **Clinical trials**
  - In the case of unapproved medical products, trials are intended to learn about safety & efficacy of product – research

- **Non-trial preapproval access** – treatment
  - Expanded Access
  - Right to Try
  - Emergency Use Authorization (CBRN emergency only)

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EA Terminology & Requirements:

"Expanded Access"
"Compassionate Use"
"Managed Access"
"Special Access"
"Named Patient Program"

Mechanism that enables patients with an unmet medical need to gain access to an unapproved medical product when they are unable to enter a clinical trial

- Serious or life threatening condition
- No approved alternative available
- Cannot interfere with clinical development
- Positive benefit/risk assessment for patient

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EA can be for a single patient or cohort; sponsored by a physician or a product developer

- RWD may be collected from both
- Volume of physician-submitted requests from FY 2019 for EA

Cohort EA

Expanded Access INDs		Individual (Single) Patient Non-Emergency IND		Individual (Single) Patient Emergency IND		Intermediate Size IND		Treatment IND	
		received	allowed to proceed	received	allowed to proceed	received	allowed to proceed	received	allowed to proceed
FY 2019	CDER	1083	1080	366	366	20	18	4	1
	CBER	101	100	141	140	3	2	2	2

- Same time period, except with the support of product sponsors:

Expanded Access Protocols		Individual (Single) Patient Non-emergency Protocol		Individual (Single) Patient Emergency Protocol		Intermediate Size Protocol		Treatment Protocol	
		received	allowed to proceed	received	allowed to proceed	received	allowed to proceed	received	allowed to proceed
FY 2019	CDER	28	28	21	21	14	13	18	18
	CBER	52	52	33	33	5	4	4	4

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https://www.fda.gov/news-events/expanded-access/expanded-access-compassionate-use-submission-data

EA is *treatment*, not *research*
*(*albeit treatment with a medical product that hasn't been proven safe or effective for any indication)

Product recipient is expecting their well-being to be the primary concern, not data collection

but, especially with rare diseases, any data collection may be valuable!

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RWD collected from EA *can…*

- generate hypotheses or inform the design of an RCT
- identify biomarkers
- determine characteristics for stratification when randomizing
- provide safety information

…*If* the EA data is fit for purpose

- was data collection reliable/accurate/rigorous?
- Is the data generalizable to another group?
- Is the data especially subject to bias (above and beyond not being randomized?
- What is the quantity of data?

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Case study: FDA approval based on EA data

Review > Clin Cancer Res. 2016 Sep 15;22(18):4545-9.
doi: 10.1158/1078-0432.CCR-16-0638. Epub 2016 Jul 11.

FDA Approval: Uridine Triacetate for the Treatment of Patients Following Fluorouracil or Capecitabine Overdose or Exhibiting Early-Onset Severe Toxicities Following Administration of These Drugs

Gwynn Ison [1], Julia A Beaver [2], W David McGuinn Jr [2], Todd R Palmby [2], Jeannette Dinin [2], Rosane Charlab [2], Anshu Marathe [2], Runyan Jin [2], Qi Liu [2], Xiao Hong Chen [2], Xavier Ysern [2], Olen Stephens [2], Ge Bai [2], Yaning Wang [2], Sarah E Dorff [2], Joyce Cheng [2], Shenghui Tang [2], Rajeshwari Sridhara [2], William Pierce [2], Amy E McKee [2], Amna Ibrahim [2], Geoffrey Kim [2], Richard Pazdur [2]

Affiliations + expand

PMID: 27401247 DOI: 10.1158/1078-0432.CCR-16-0638

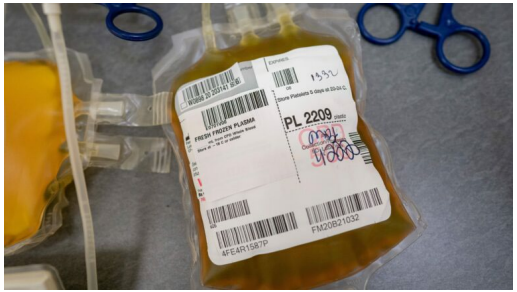
has not been established. The approval is based on data from two single-arm, open-label, expanded-access trials in 135 patients receiving uridine triacetate (10 g or 6.2 g/m(2) orally every 6 hours for 20 doses) for fluorouracil or capecitabine overdose, or who exhibited severe or life-threatening toxicities within 96 hours following the end of fluorouracil or capecitabine administration. Ninety-six percent of patients met the major efficacy outcome measure, which was survival at 30 days or survival until the resumption of chemotherapy, if prior to 30 days. The most common adverse reactions were vomiting, nausea, and diarrhea. This article summarizes the FDA

Case study: Convalescent plasma (CP)

- Idea that receiving plasma from people who have recovered from the disease can help treat Covid-19

- History of administration for the prevention and treatment of epidemic infections; however, CP has never been approved by FDA for any use (currently available via EUA)

- On April 3, 2020 FDA authorized a cohort EAP for treatment use of CP in hospitalized Covid-19 patients
  - Nationwide effort with Mayo Clinic as coordinating site; reviewed by Mayo Clinic IRB
  - Real world data were collected



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CP EAP largest in U.S. history

- Infusion of >94,000 patients
- For comparison, the largest prior EAPs (e.g., lamivudine-HIV, gefitinib-cancer) each provided unapproved drugs to ~30,000 patients
- By regulation, EAPs are not supposed to hinder launching clinical trials
  - Many clinical trials of CP failed to fully accrue (argument re whether all sites that participated in EAP could have hosted clinical trials)
- Efficacy results from EA did not align with subsequent RCT results

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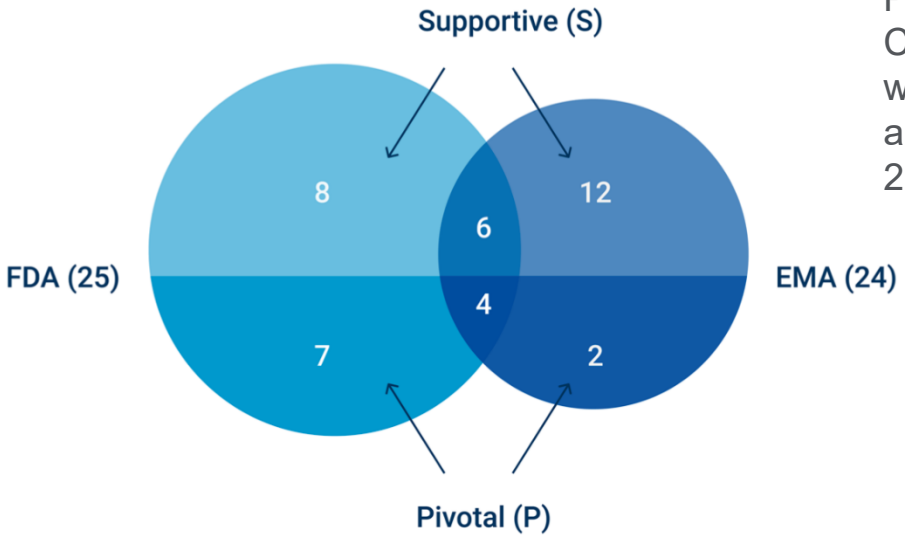
Biopharmaceutical industry increasingly interested in collecting RWD from EA; Regulators increasingly willing to consider these data in regulatory submissions; also payers



Polak TB, van Rosmalen J, Uyl-de Groot CA. Expanded Access as a source of real-world data: An overview of FDA and EMA approvals. *Br J Clin Pharmacol*. 2020;86(9):1819-1826.

FIGURE 3 Venn-diagram of approvals where the Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) relied on data from expanded access programmes to form the clinical efficacy profile. The level of evidence associated to these data by either regulator could be pivotal or supportive

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Conclusion

Sponsors, regulators, and payers all see utility in real world data from EA,
but we must not oversell its potential.

This data can demonstrate safety findings, and it may provide the best possible efficacy data when this can not be otherwise collected; but is likely not able to replicate the findings of a randomized control trial and thus should be viewed as hypothesis-generating and/or supplemental when RCTs are possible.

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Thank you

I'd like to acknowledge that in this presentation I leaned on the shared knowledge and research of the NYU Working Group on Compassionate Use and Preapproval Access (CUPA) members.

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