Translational Pharmacoinformatics: Developing an Integrated Central Resource for Planning HCV Drug Interactions Research

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ACTG AIDS CLINICAL TRIALS GROUP

New York State Center of Excellence in Bioinformatics & Life Sciences

Translational Pharmacoinformatics:

- Translational:
  - Pre-clinical → Clinical → Post-approval
- Pharmacoinformatics:
  - Use of information technology to assimilate drug information
  - Drug Development context:
    - Information technology to facilitate drug development

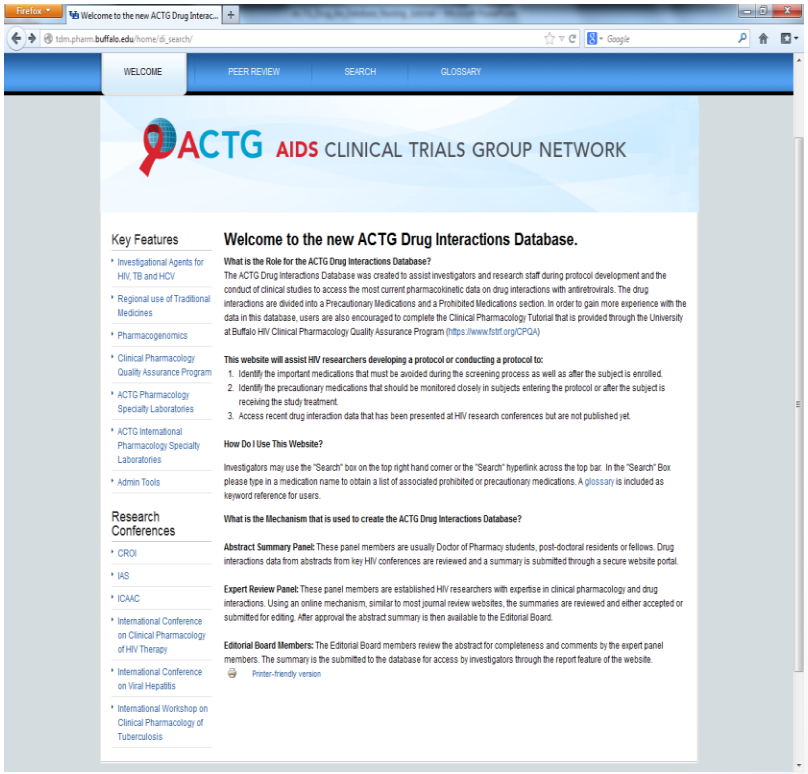
ACTG Precautionary and Prohibited Medications Database

- Clinical research in the areas of HIV, Viral Hepatitis, TB and Inflammation presents:
  - Challenges in reviewing new drug interaction and pharmacokinetic data for protocol development
  - Potential for clinically significant interactions between these medications and commonly prescribed drugs

- The ACTG developed a *Precautionary and Prohibited Medications Database* resource in response to these challenges.

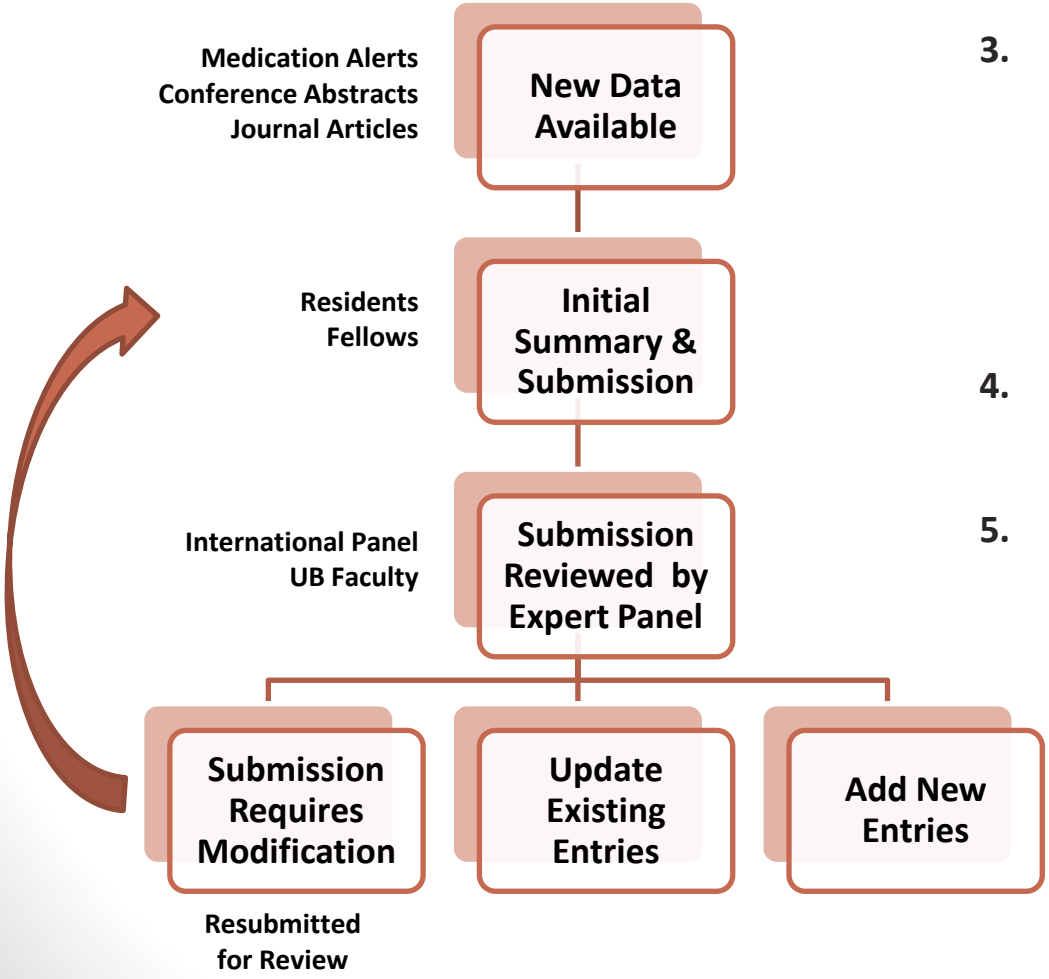
ACTG Precautionary and Prohibited Medications Database

- Maintained by the University at Buffalo Pharmacology Specialty Laboratory (UB PSL)
- Utilized by ACTG and IMPAACT investigators
- Originally focused on drug-drug interactions between ARVs and non-ARVs
  - Expanded to include agents for:
    - Tuberculosis
    - Viral Hepatitis
- International expert review panel and editorial board created
  - ACTG Clinical Pharmacology Advisory Group (CPAG)
  - Review of newly available drug interaction and PK data presented in abstract form



https://actgnetwork.org/

Database Update Process



1. Drug interactions and PK data available from conferences, journals, and industry
2. Data summarized and uploaded to non-searchable database
   a. Multiple sources may be used for a single drug-drug interaction entry
3. Summary assigned to and reviewed by clinical pharmacology expert
   a. Accepted as submitted
   b. Revisions required
      i. Repeat submission / initial review process
4. Final acceptance approved by managing content editor
5. Summary made available on searchable database
   a. Interpretation of data
   b. Interaction designation
      i. Precautionary or prohibited
   c. References available

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ACTG Drug Interactions Database

...the Clinical Protocol Development Tool for Precautionary and Prohibited Medication Use

WELCOME | PEER REVIEW | SEARCH | GLOSSARY

ACTG AIDS CLINICAL TRIALS GROUP NETWORK

Home

Key Features

- Investigational Agents for HIV, TB and HCV
- Regional use of Traditional Medicines
- Pharmacogenomics
- Clinical Pharmacology Quality Assurance Program
- ACTG Pharmacology Specialty Laboratories
- ACTG International Pharmacology Specialty Laboratories
- Admin Tools

INSTRUCTIONS: To search for a specific ARV drug and a concomitant medication please separate drug names by semi-colon (example: phenytoin; delavirdine). SEE FULL INSTRUCTIONS . You can also use the Keywords Glossary as keyword reference.

Search

Enter your keywords:

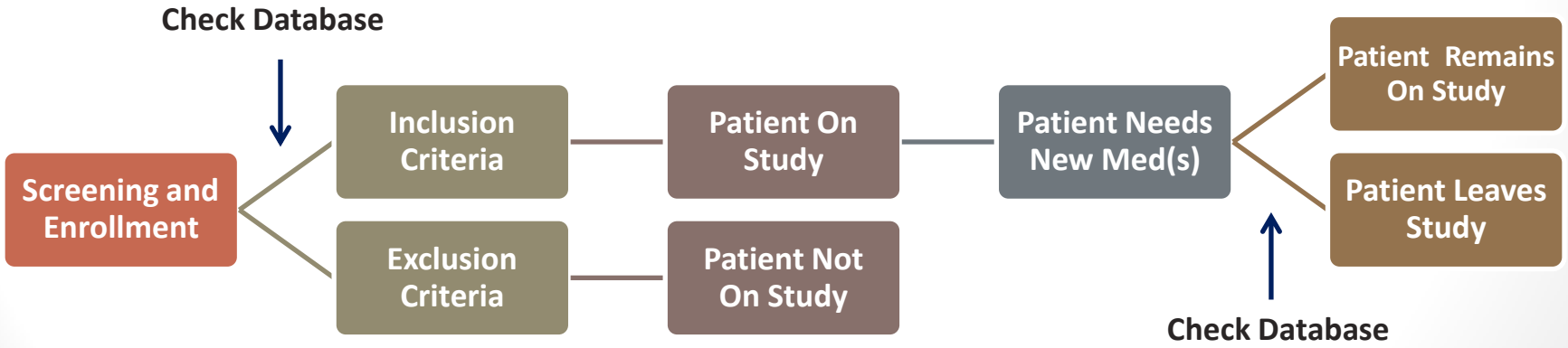
raltegravir; omperazole

SEARCH

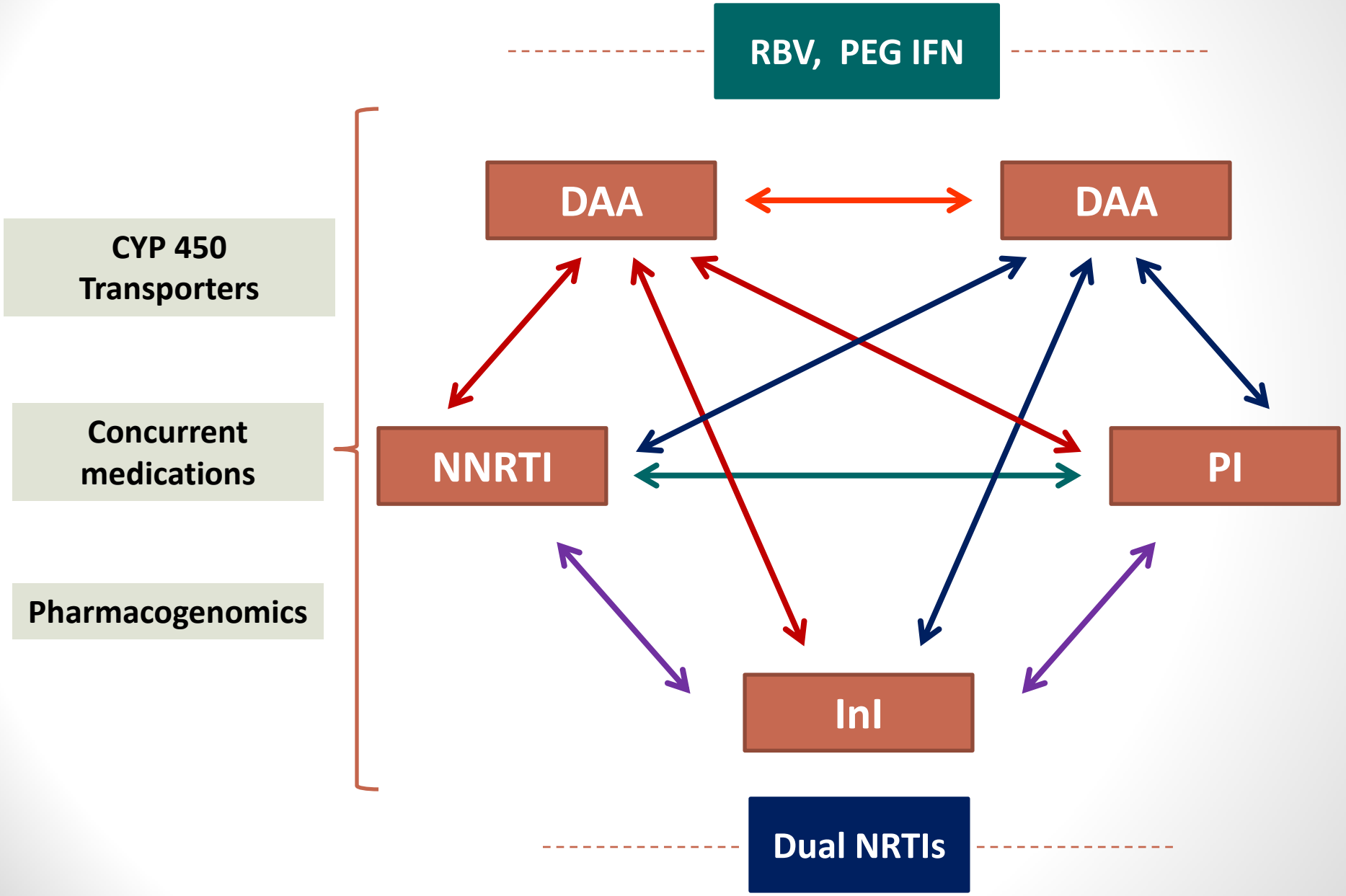
Applications

Protocol Development and Human Subject Protection

- Protocol team accesses Precautionary and Prohibited Medications
- Protocol investigators access database from ACTG homepage
  - Check for drug-drug interactions among study medications
    - At enrollment
    - During study as needed



Co-Infection: Complex Drug-Drug Interactions



Approved DAAs

Drug	CYP450 Activity		Transporters	
	Substrate	Inhibitor	Substrate	Inhibitor
Telaprevir	CYP3A4	CYP3A4*	P-gp	P-gp OATP1B1 OATP2B1
Boceprevir	CYP3A4/5+	CYP3A4/5*	P-gp	P-gp

*Strong; +Partial (BOC primarily metabolized by AKR)

Medications extensively metabolized by CYP3A and associated with severe adverse reactions at high concentrations are not recommended for coadministration with boceprevir or telaprevir. [1,2]

[1]Victrelis package insert, Merck & Co, Inc., 2013; [2]Incivek package insert, Vertex Pharmaceuticals Incorporated, December 2012

DAAs in Development

Drug	CYP Activity	Transporters	Phase (as a single agent)
Daclatasvir*+	CYP3A4 substrate[3]	P-gp substrate[3]	III
Faldaprevir*+	CYP 3A4 substrate 3A4: Moderate intestinal and hepatic inhibition *in vivo*[4]		III
Sofosbuvir*		(Renal excretion)[5]	III

*Also studied in combination with other DAAs; +Also studied in combination with ARVs

[3]Bifano M et al. CROI 2012. Abstract 618.; [4]Sabo J et al. CROI 2013. Abstract 35.; [5]Cornpropst M et al. EASL 2012.

DAAs in Development

Drug	CYP Activity	Transporters	Phase (as a single agent)
Ledipasvir*	No CYP inhibition *in vivo*[6]		III
Simeprevir*+	CYP3A4 substrate[7] 3A4: Mild intestinal inhibition; no hepatic inhibition[8]	P-gp substrate P-gp: Mild intestinal inhibition; no hepatic inhibition	III

*Also studied in combination with other DAAs; +Also studied in combination with ARVs

[6]Lawitz E et al. J Hepatol. 2012 Jul;57(1):24-31.; [7]Ouwerkerk-Mahadevan S et al. IDSA 2012. Abstract 36620.;
[8]Sekar V et al. EASL 2010. Poster 1076.

DAAs-ARVs in Combination

DAA	DAA + ARV Effects on Concentrations							
	PI[12]		NNRTI[13,14,15]		InSTI[16]		Other[13]	
Boceprevir	↓ ATV/r*	↓ BOC	↓ EFV*	↓ BOC	↔ RAL	BOC+	↑ TFV	↔ BOC
	↓ LPV/r*	↓ BOC	↓ ETV	↓ BOC				
	↓ DRV/r*	↓ BOC	↑ RPV	↓ BOC				
	PI[17,18]		NNRTI[18,19,20]		InSTI		Other[18]	
Telaprevir	↑ ATV/r	↓ TVR	↓ EFV	↓ TVR	---	---	↑ TDF	↔ TVR
	↓ DRV/r#	↓ TVR	↔ ETV	↓ TVR				
	↓ LPV/r#	↓ TVR	↑ RPV	↓ TVR				
	↓fAPV/r#	↓ TVR						

ATV=atazanavir; LPV/r=lopinavir/ritonavir; DRV=darunavir; fAPV=fosamprenavir; EFV=efavirenz; ETV=etravirine; RPV=rilpivirine; RAL=raltegravir; TFV=tenofovir; TDF=tenofovir disoproxil fumarate; BOC=boceprevir; TVR=telaprevir

+Effect on concentration not reported

*Not recommended for coadministration with BOC

#Not recommended for coadministration with TVR

[12]Hulskotte E et al. CROI 2012. Paper 771LB; [13]Kasserra C et al. CROI 2011. Paper 118.; [14]Hammond K et al. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):67-73; [15]Rhee E et al. CROI 2013. Abstract 537.; [16]de Kanter C et al. CROI 2012. Paper 772LB.; [17]Garg V et al. CROI 2011. Paper 629.; [18]van heeswijk et al. CROI 2011. Paper 119.; [19]Garg V et al. Intl Wrkshp Clin Pharm HIV Ther 2011. Abstract PK_13.; [20]Kakuda T et al. Intl Wrkshp Clin Pharm HIV Ther 2012. Abstract O_18.

DAAs-ARVs Studied in Combination

DAA	DAA + ARV Effects on Concentrations							
	PI[21]		NNRTI[21]		InSTI		Other[21]	
Daclatasvir	↔ATV/r	↔ DCV*	↔ EFV	↔ DCV*	---	---	↔ TDF	↔ DCV
	PI[22]		NNRTI[22]		InSTI		Other[22]	
Faldaprevir	↔DRV/r	↑ FDV	EFV+	↓ FDV	---	---	↔ TFV	↓ FDV
	PI[23]		NNRTI[23,24]		InSTI[23,24]		Other[23]	
Simeprevir	↔DRV/r	↑ SPV	↔ EFV	↓ SPV	↔ RAL	↔ SPV	↔ TDF	↔ SPV
			↔ RPV	↔ SPV				

ATV=atazanavir; DRV=darunavir; EFV=efavirenz; ETV=etravirine; RPV=rilpivirine; RAL=raltegravir; TFV=tenofovir; TDF=tenofovir disoproxil fumarate; DCV=daclatasvir; FDV=faldaprevir; SPV=simeprevir

*No change in concentration expected at normalized DCV doses

+Effect on concentration not reported

[21]Bifano M et al. CROI 2012. Paper 618.; [22]Sabo J et al. CROI 2013. Abstract 35.; [23]Ouwerkerk-Mahadevan S et al. IDSA 2012.; [24]Ouwerkerk-Mahadevan S et al. CROI 2012. Paper 49.

DAAs in Combination

DAAs	Phase	Population	Notes	w/ ARVs
Daclatasvir + Sofosbuvir	II[9]	HCV monoinfection	+/- RBV	-----
	II	HCV monoinfection	+/- RBV; Genotypes 2 & 3	-----
Daclatasvir + Simeprevir	II	HCV monoinfection	+/- RBV; + additional PEG-IFN & RBV if needed	-----
Sofosbuvir + Simeprevir	II[10]	HCV monoinfection HCV monoinfection		-----
Sofosbuvir + Ledipasvir	II	HCV monoinfection	Genotype 4	-----
	II[11]	HCV monoinfection		-----
Daclatasvir + Asunaprevir	II	HCV-HIV co-infection	Genotype 1 or 4; Null responders; +RBV & PEG IFN	Raltegravir Tenofovir Enfuvirtide Emtricitabine Lamivudine Abacavir

[9]Sulkowski MS et al. AASLD 2012. Abstract LB-2.; [10]Lawitz E et al. CROI 2013. Abstract 155LB; [11]Gane E et al. AASLD 2012. Abstract 229.

Summary

- The ACTG Prohibited and Precautionary Medications Database is *well established* and is a resource for investigators developing and implementing research protocols.
- The Database has the *potential to be a wider resource* and facilitate planning for drug interactions research but would require:
  - Additional input of pre-clinical drug interactions and PK data
  - Drug interactions data not presented at conferences
- The database could provide a mechanism to *avoid duplication of research studies while identifying "gap" areas* that could form the basis of investigator-initiated research or RFAs.
- *Post-approval data collection* could be included as a mechanism to confirm or refute "healthy volunteer PK studies.

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