Resource Implications of IOM Recommendations for Trial Registration and Results Database

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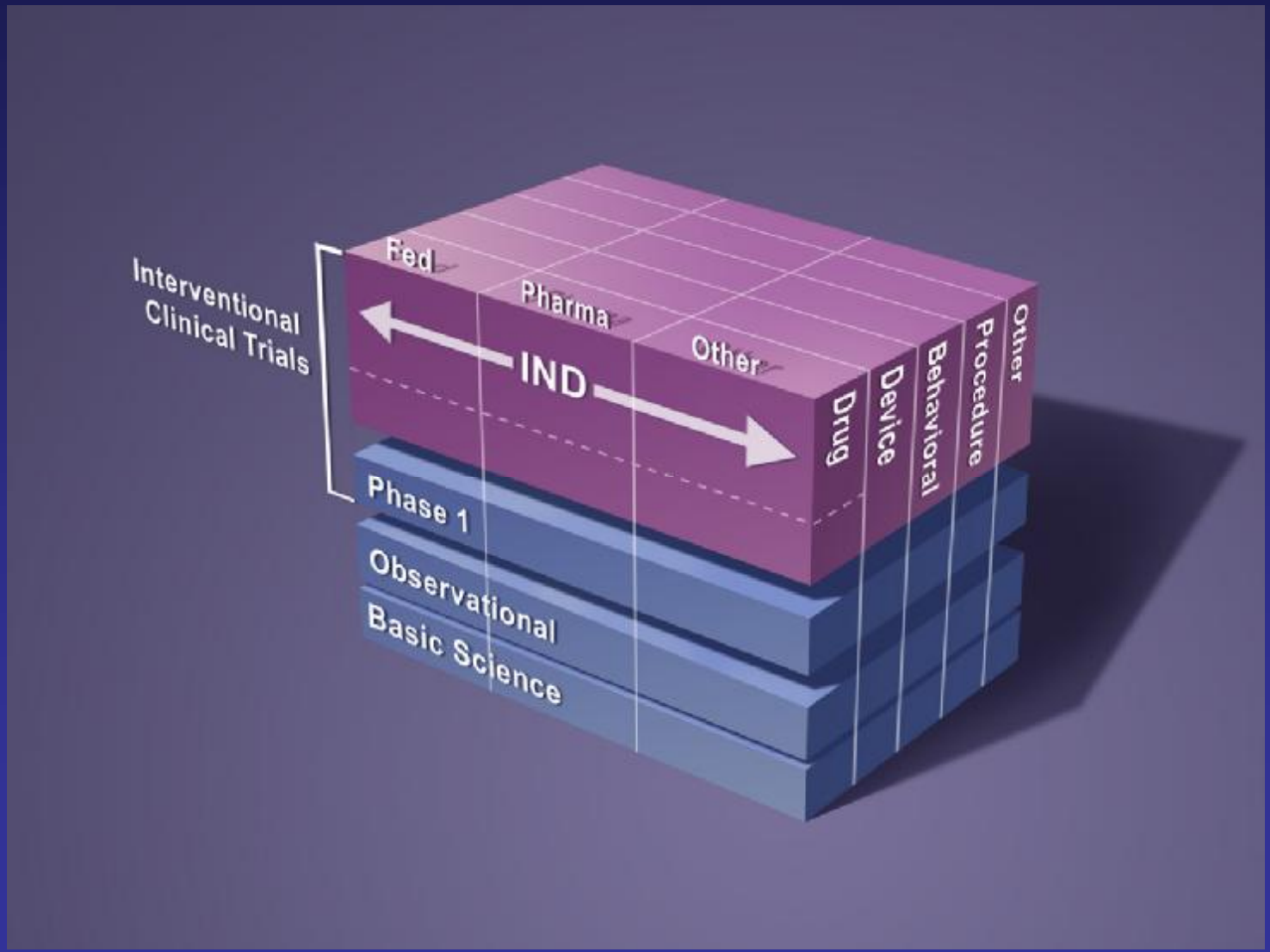
Key IOM Recommendations

1. Expand scope of mandatory registration
2. Add results
3. Scientific Review
4. Monitoring and Enforcement

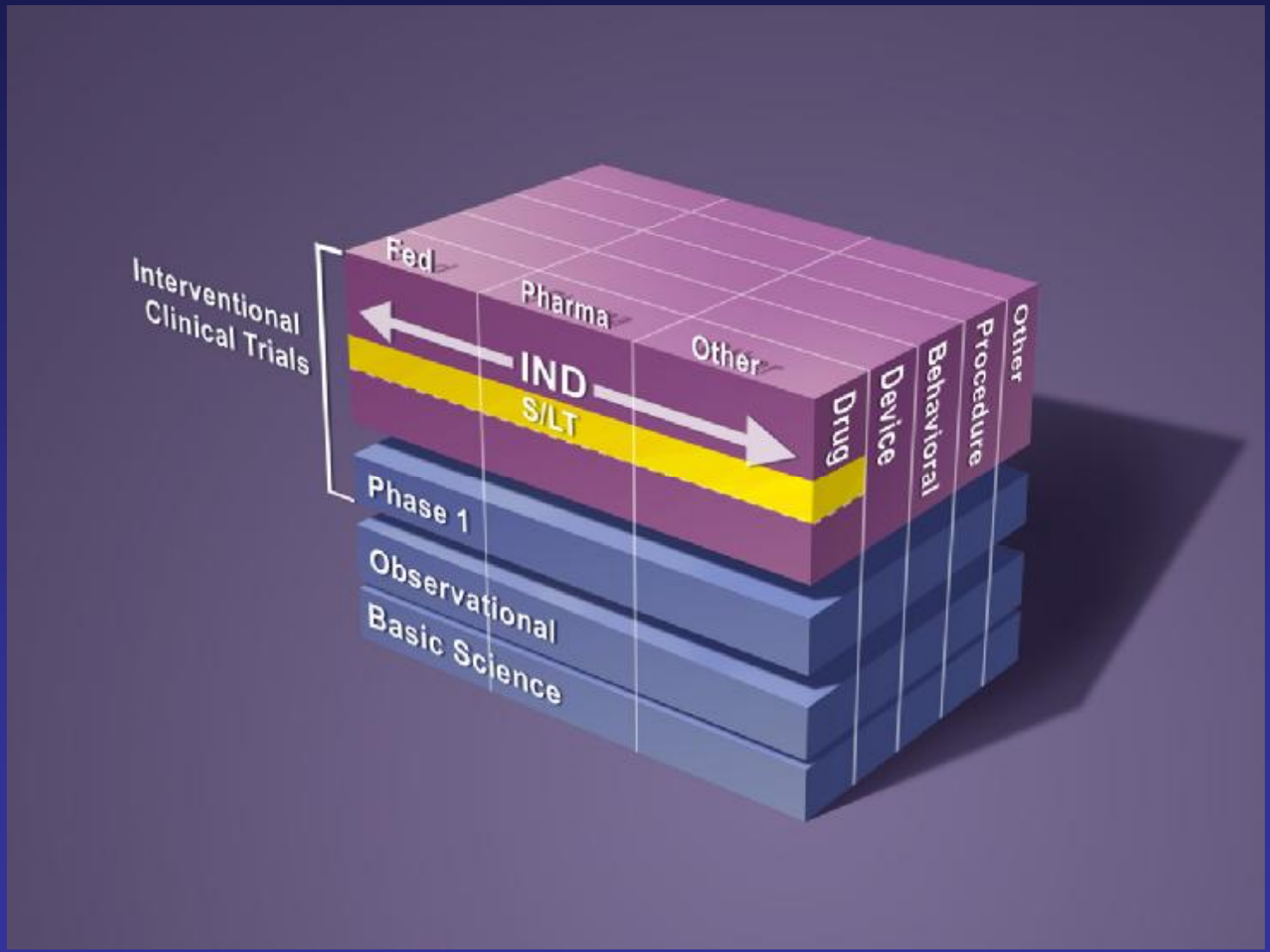
Recommendation #1: Expand Scope of Registry

- Industry, phase 2-4 drug studies
- “note with interest” other policy initiatives

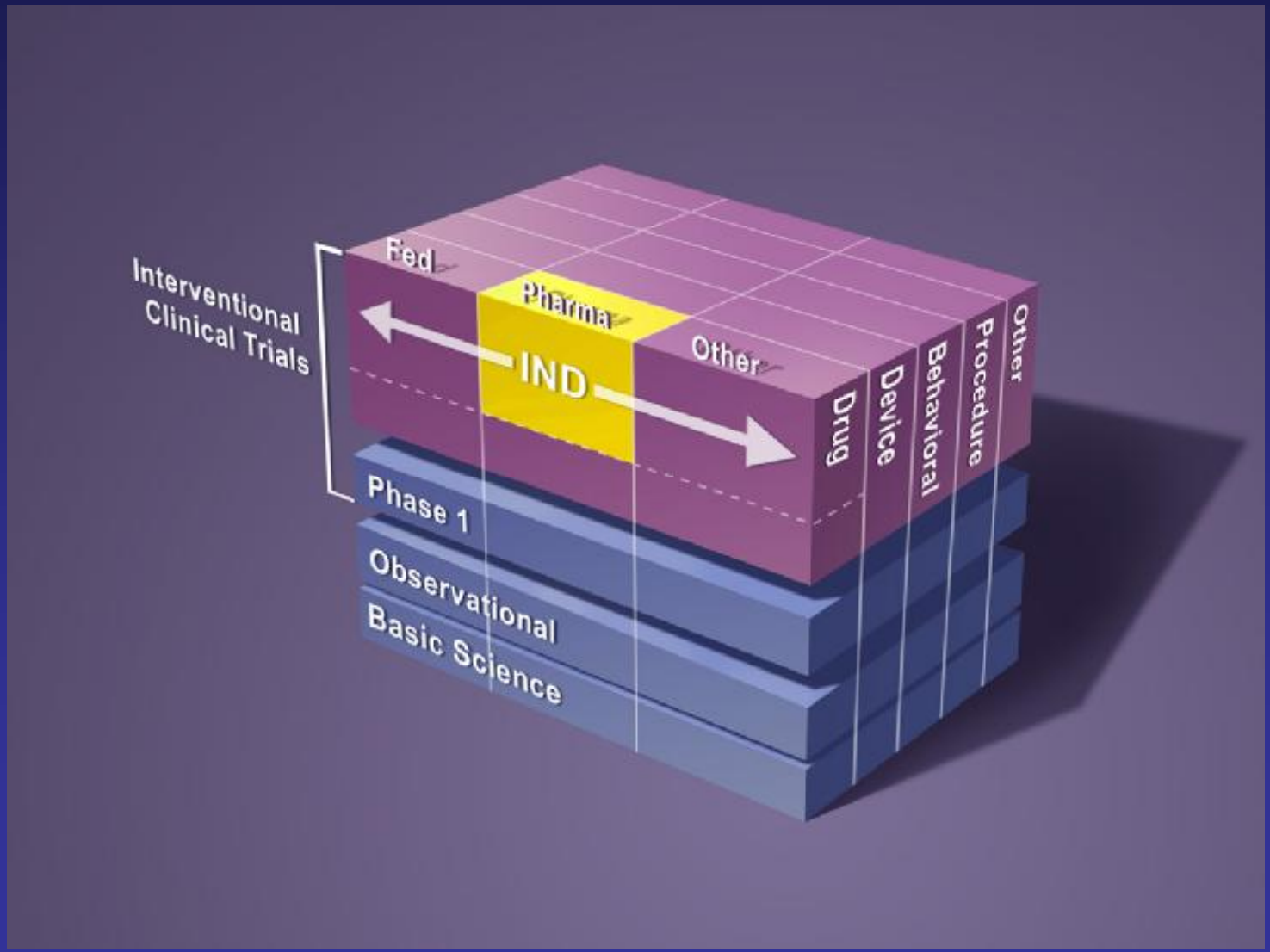
“Clinical Trials”



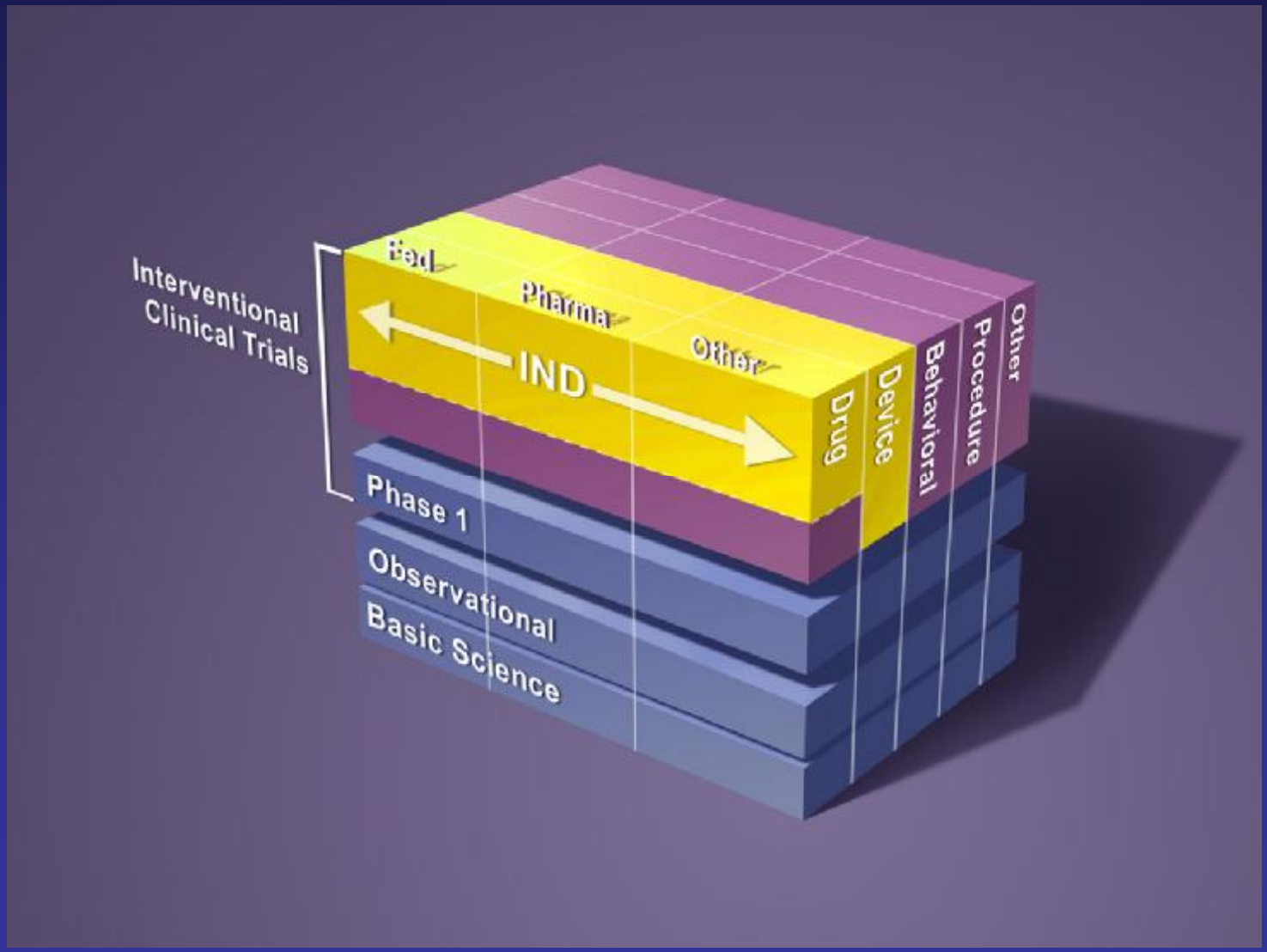
Scope of FDAMA



Scope of IOM, Enzi-Kennedy

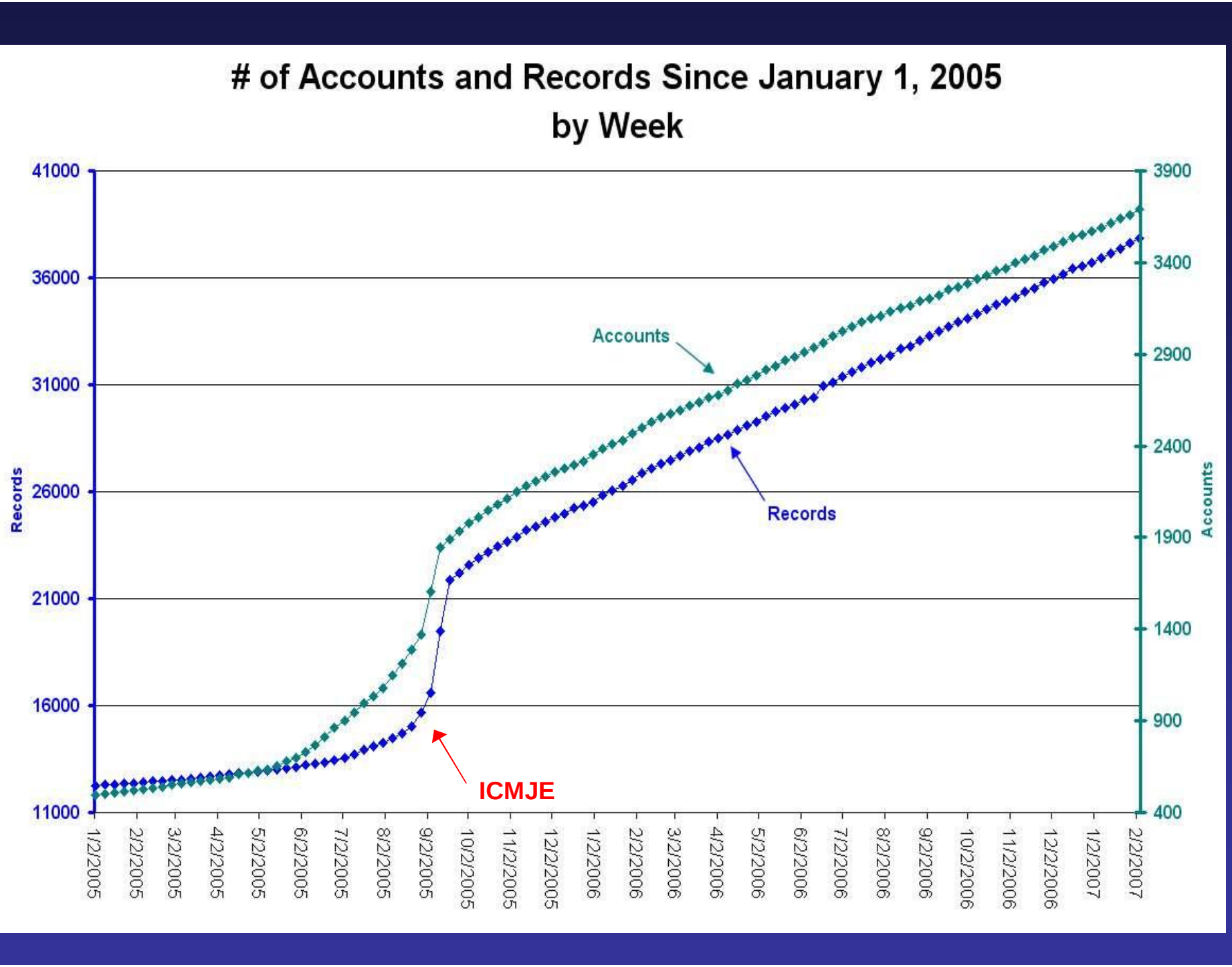


Scope of FACT Act



Resource Implications: Expanded Registry

- Currently > $3 million
- Dependent on rest of NLM (>$300 million)
  - E.g., search engine, hardware, personnel, etc.
- Can handle large increases in # of trials


# of Accounts and Records Since January 1, 2005
by Week
Records
Accounts
41000
36000
31000
26000
21000
16000
11000
3900
3400
2900
2400
1900
1400
900
400
Accounts
Records
ICMJE
1/2/2005
2/2/2005
3/2/2005
4/2/2005
5/2/2005
6/2/2005
7/2/2005
8/2/2005
9/2/2005
10/2/2005
11/2/2005
12/2/2005
1/2/2006
2/2/2006
3/2/2006
4/2/2006
5/2/2006
6/2/2006
7/2/2006
8/2/2006
9/2/2006
10/2/2006
11/2/2006
12/2/2006
1/2/2007
2/2/2007

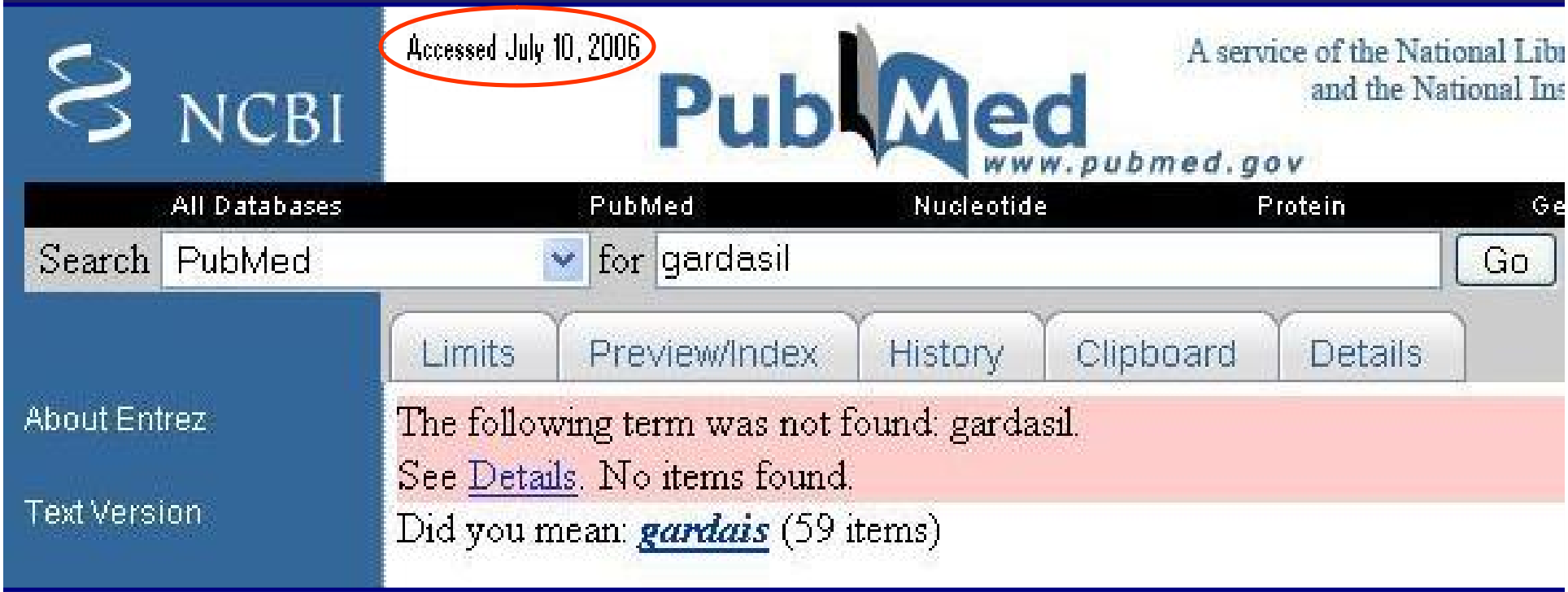
Key Functions that are affected by policy decisions

- Are the mandated trials registered?
  - Objective criteria are best
- Is the information meaningful?
  - Provide NIH flexibility to define “acceptable” entries
- Can users find the trials they want?
  - 20% industry drug records use serial numbers that are not tracked by any external agency

Drug Serial Numbers: “hidden” trials

Gardasil® was approved on June 8, 2006

Pubmed Gardasil Search – one month after approval (and promotion)



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Linking patients to medical research

Developed by the National Library of Medicine

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Gardasil (V501) Study in Adult Women

This study is currently recruiting patients.

Verified by Merck September 2006

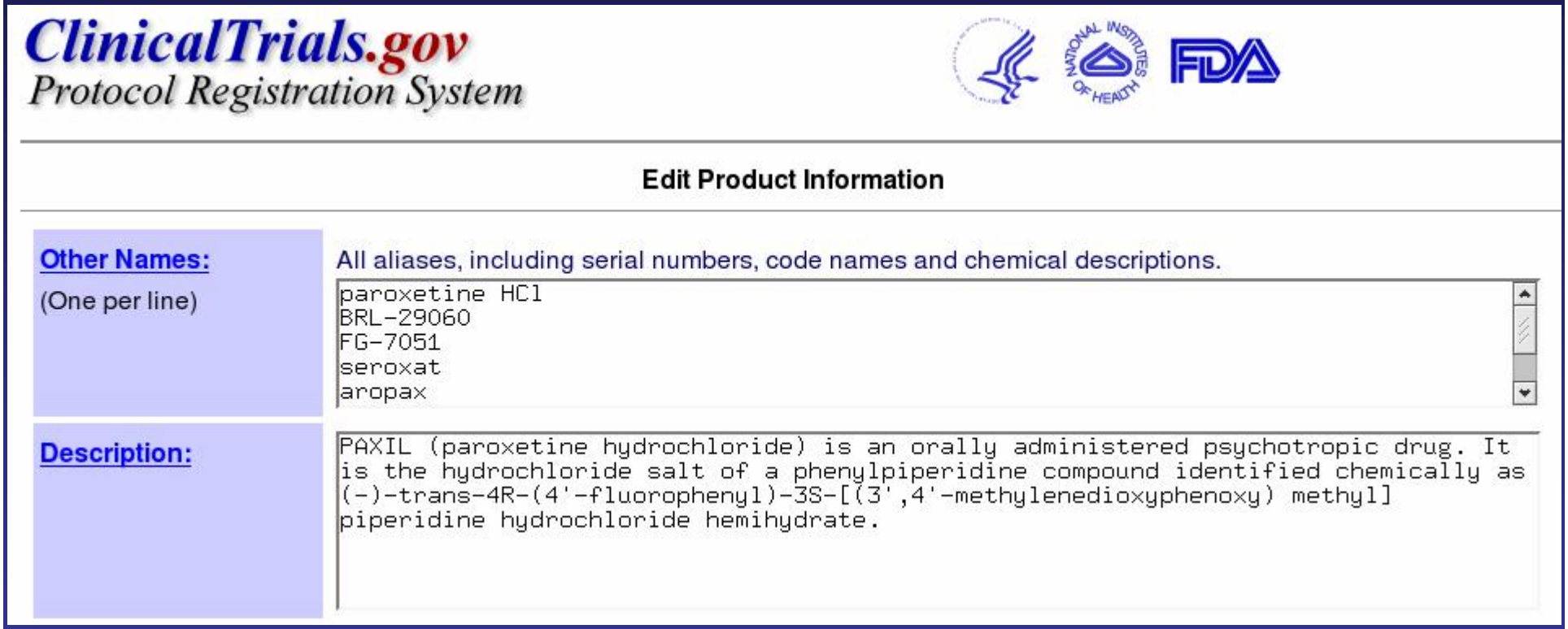
Sponsored by:	**Merck**
Information provided by:	Merck
ClinicalTrials.gov Identifier:	NCT00378560

Purpose

A study to evaluate the efficacy, immunogenicity, safety and tolerability of Gardasil (V501) in adult women.

Condition	Intervention	Phase
Papillomavirus Infections	Vaccine: V501, Gardasil, human papillomavirus (types 6,11,16,18) recombinant vaccine / Duration of Treatment: 7 Months Vaccine: Placebo (unspecified) / Duration of Treatment: 7 Months	Phase II

Potential Impact of a Policy (Maine)



ClinicalTrials.gov
Protocol Registration System

Edit Product Information

Other Names:
(One per line)

All aliases, including serial numbers, code names and chemical descriptions.

```
paroxetine HCl
BRL-29060
FG-7051
seroxat
aropax
```

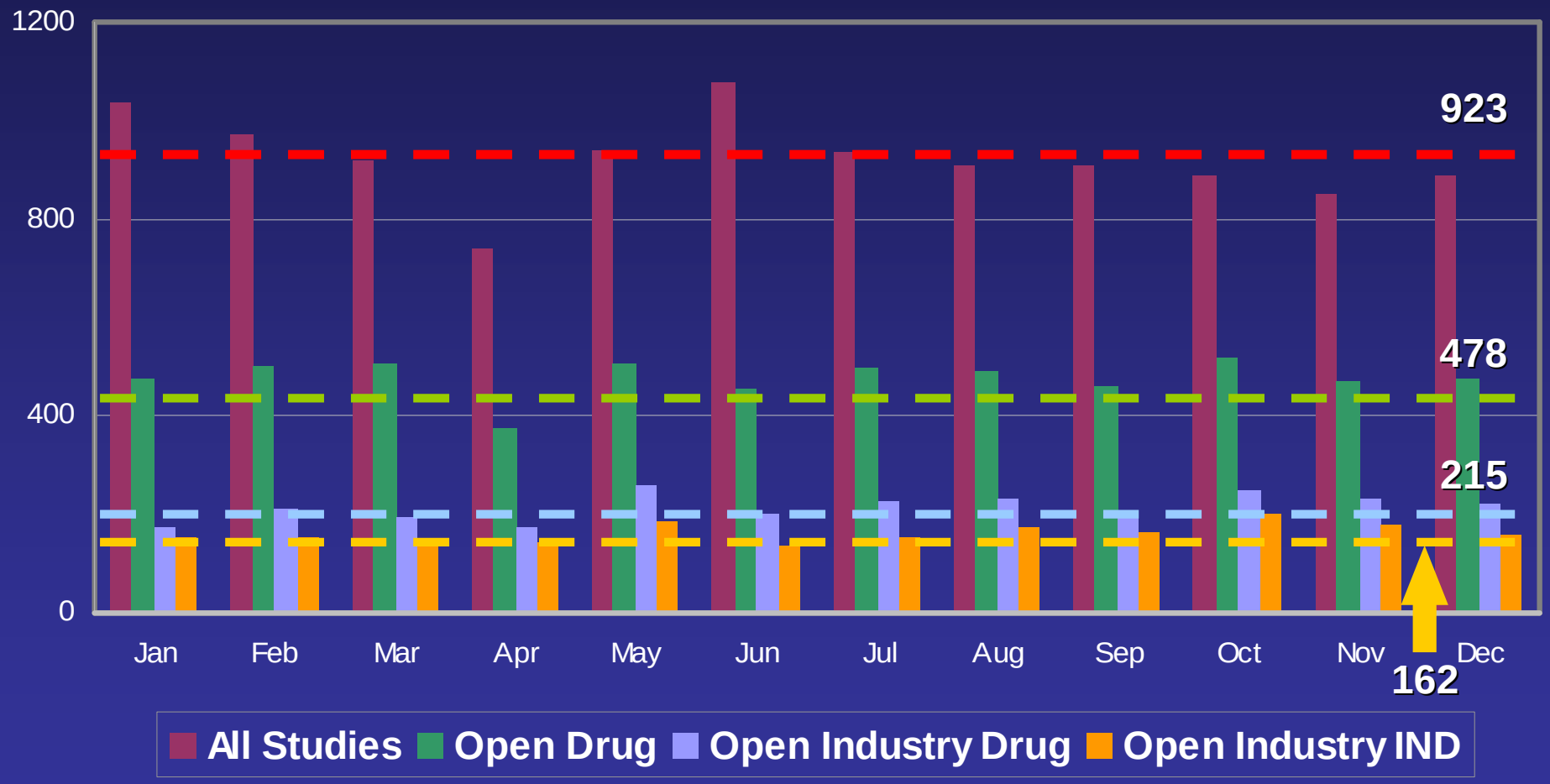
Description:

```
PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It
is the hydrochloride salt of a phenylpiperidine compound identified chemically as
(-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl]
piperidine hydrochloride hemihydrate.
```

Recommendation #2: Add a Results Database

- We already link to published results
- We could link to drugs@fda if trial identifiers were used
- For de novo results reporting, QA is complex
- Resource needs will be dependent on # trials
- Validation will be “challenging”

Trials received by ClinicalTrials.gov in 2006



Validation of Data for Registry

- System of automated and manual checks
- “Due diligence” but errors may occur
- Errors are corrected when found
- Archive site tracks changes

Possible Error in Registry that would be difficult to detect

Primary Outcomes: Change in depressed mood scores immediately following the 3 month intervention and at 3 and 6 months post-treatment,; as measured by the Edinburgh Postnatal Depression Scale and the Hamilton Rating Scale for Depression.

Secondary Outcomes: Changes in fatigue levels (measured by the multidimensional fatigue inventory), sleep patterns, anxiety and health status.

Validation of Data in Results Database

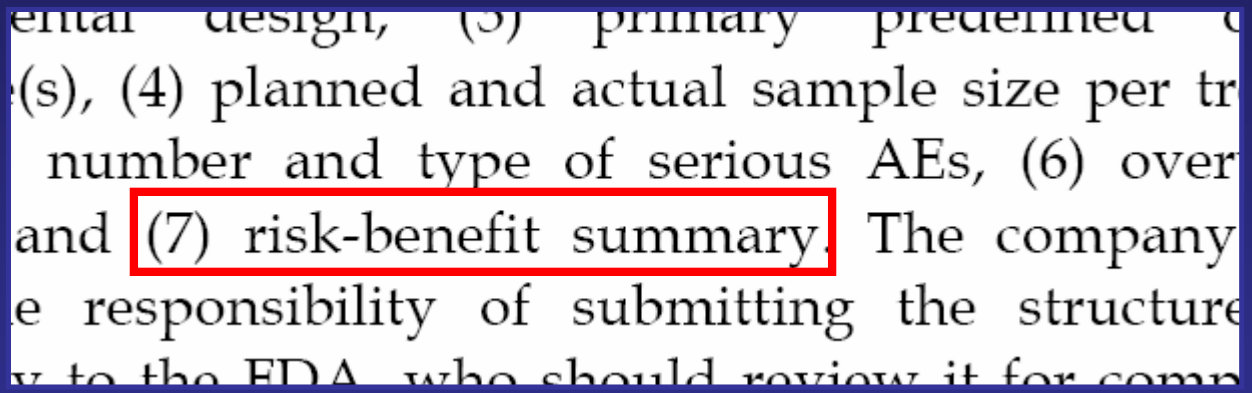
- Data are more complex, and stakes are higher
- No proposals provide access to protocol or source data

Possible Error in Results Database that would be difficult to detect

Mean change from baseline	50mcg	100mcg	Placebo
Baseline – Mean (SE)	n=100 1.63 (0.04)	n=97 1.57 (0.04)	n=96 1.65 (0.04)
p-value versus placebo	0.998	0.348	-
Change from Baseline at Endpoint – Mean (SE)	n=98 0.20 (0.02)	n=97 0.25 (0.03)	n=96 0.09 (0.03)
p-value versus placebo	0.004	<0.001	-

IOM recommendation

- In addition to structured data:

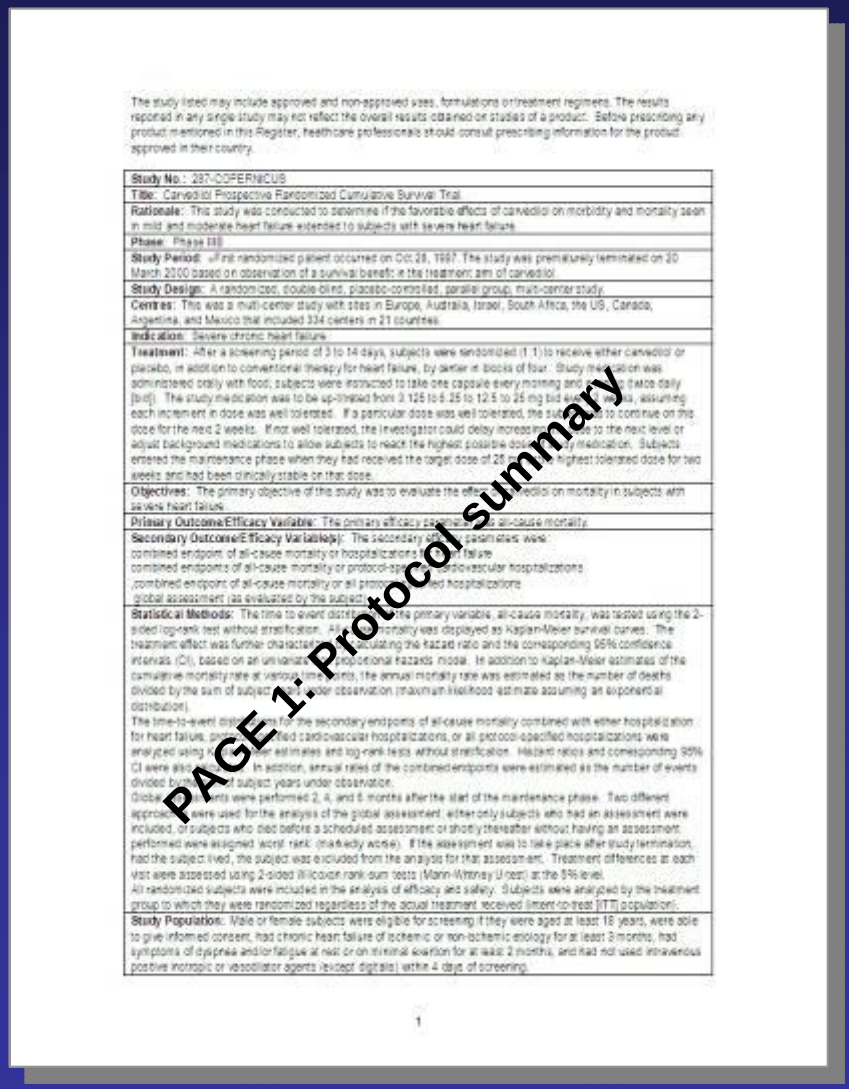


Recommendation #3: Scientific Review

- FDA: ensure accuracy and completeness of “structured field summary”
  - Between 40 and 200+ trials/week
- NIH: develop “editorial process” for “other data”

GSK results entry: COPERNICUS

- COREG (Carvedilol) in preventing death of patients with severe heart failure
- Primary outcome was all-cause mortality
- Stopped early by DMC for benefit at the 4th interim analysis
- Results are published on GSK website
  - 1 page of protocol and analysis methods
  - 1.5 pages of results in tabular format



The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 287-COPERNICUS

Title: Carvedilol Prospective Randomized Cumulative Survival Trial

Rationale: This study was conducted to determine if the favorable effects of carvedilol on morbidity and mortality seen in mild and moderate heart failure extended to subjects with severe heart failure.

Phase: Phase III

Study Period: ...irst randomized patient accrued on Oct 28, 1997. The study was prematurely terminated on 20 March 2000 based on observation of a survival benefit in the treatment arm of carvedilol.

Study Design: A randomized, double-blind, placebo-controlled, parallel group, multi-center study.

Centres: This was a multi-center study with sites in Europe, Australia, Israel, South Africa, the US, Canada, Argentina, and Mexico that included 334 centers in 21 countries.

Indication: Severe chronic heart failure.

Treatment: After a screening period of 3 to 14 days, subjects were randomized (1:1) to receive either carvedilol or placebo, in addition to conventional therapy for heart failure, by center in blocks of four. Study medication was administered orally with food; subjects were instructed to take one capsule every morning and ...g twice daily (bid). The study medication was to be up-titrated from 3.125 to 6.25 to 12.5 to 25 mg bid ...s, assuming each increment in dose was well tolerated. If a particular dose was well tolerated, the subject ... to continue on this dose for the next 2 weeks. If not well tolerated, the investigator could delay increasing ... to the next level or adjust background medications to allow subjects to reach the highest possible dose ... medication. Subjects entered the maintenance phase when they had received the target dose of 25 ... highest tolerated dose for two weeks and had been clinically stable on that dose.

Objectives: The primary objective of this study was to evaluate the effect ...edilol on mortality in subjects with severe heart failure.

Primary Outcome/Efficacy Variable: The primary efficacy parameter was all-cause mortality.

Secondary Outcome/Efficacy Variable(s): The secondary efficacy parameters were:
combined endpoint of all-cause mortality or hospitalizations for heart failure
combined endpoints of all-cause mortality or protocol-spe... cardiovascular hospitalizations
combined endpoint of all-cause mortality or all protocol-specified hospitalizations
global assessment (as evaluated by the subject)

Statistical Methods: The time to event distribution for the primary variable, all-cause mortality, was tested using the 2-sided log-rank test without stratification. All-cause mortality was displayed as Kaplan-Meier survival curves. The treatment effect was further characterized by calculating the hazard ratio and the corresponding 95% confidence intervals (CI), based on an univariate Cox proportional hazards model. In addition to Kaplan-Meier estimates of the cumulative mortality rate at various time points, the annual mortality rate was estimated as the number of deaths divided by the sum of subject years under observation (maximum likelihood estimate assuming an exponential distribution).
The time-to-event distributions for the secondary endpoints of all-cause mortality combined with either hospitalization for heart failure, protocol-specified cardiovascular hospitalizations, or all protocol-specified hospitalizations were analyzed using Kaplan-Meier estimates and log-rank tests without stratification. Hazard ratios and corresponding 95% CI were also ... In addition, annual rates of the combined endpoints were estimated as the number of events divided by the ... of subject years under observation.
Global ... ments were performed 2, 4, and 6 months after the start of the maintenance phase. Two different approaches were used for the analysis of the global assessment: either only subjects who had an assessment were included, or subjects who died before a scheduled assessment or shortly thereafter without having an assessment performed were assigned worst rank (markedly worse). If the assessment was to take place after study termination, had the subject lived, the subject was excluded from the analysis for that assessment. Treatment differences at each visit were assessed using 2-sided Wilcoxon rank-sum tests (Mann-Whitney U-test) at the 5% level.
All randomized subjects were included in the analysis of efficacy and safety. Subjects were analyzed by the treatment group to which they were randomized regardless of the actual treatment received (intent-to-treat [ITT] population).

Study Population: Male or female subjects were eligible for screening if they were aged at least 18 years, were able to give informed consent, had chronic heart failure of ischemic or non-ischemic etiology for at least 3 months, had symptoms of dyspnea and/or fatigue at rest or on minimal exertion for at least 2 months, and had not used intravenous positive inotropic or vasodilator agents (except digitalis) within 4 days of screening.

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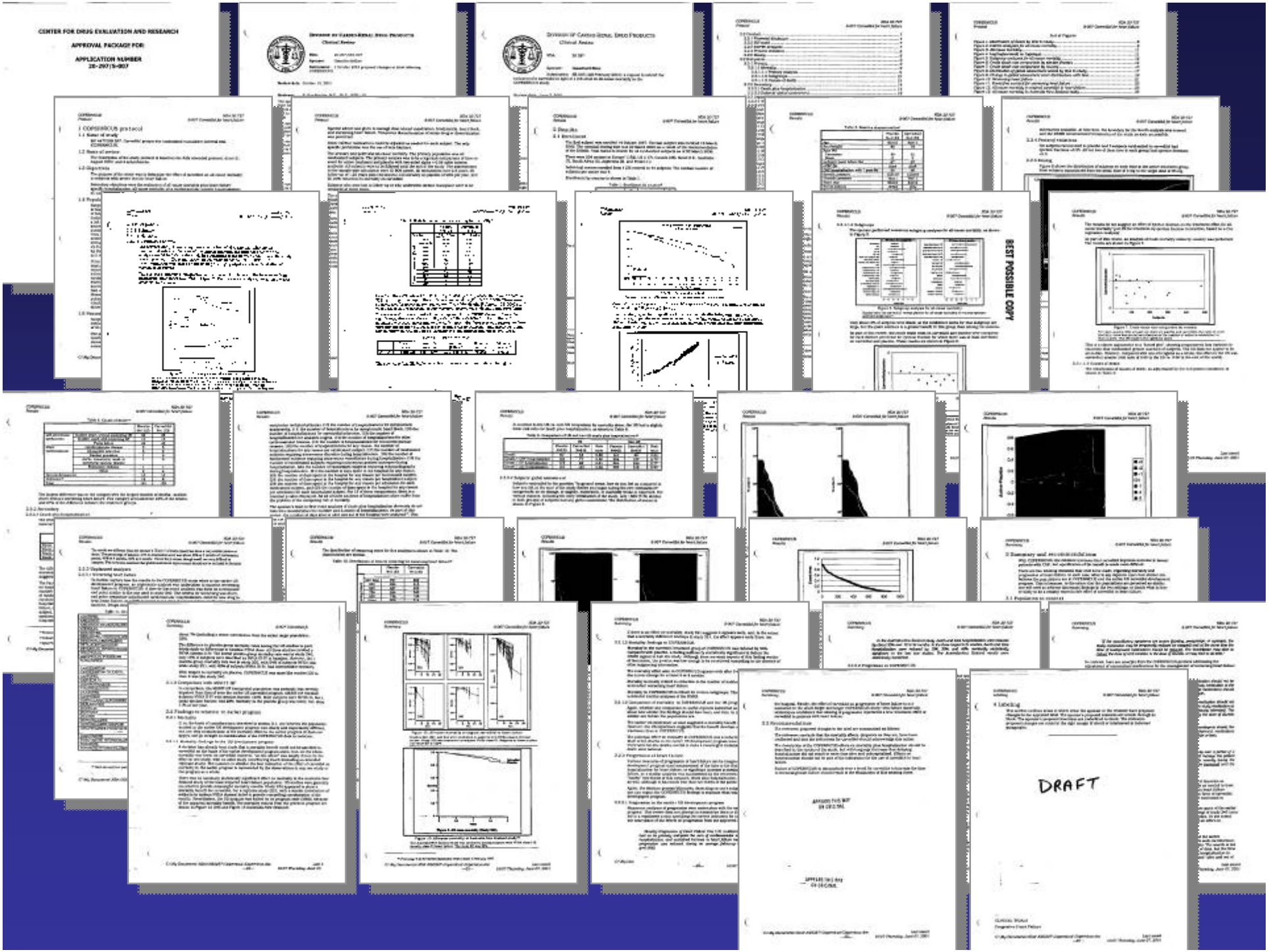
PAGE 1: Protocol summary


CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVAL PACKAGE FOR:
APPLICATION NUMBER
20-297/S-007
BEST POSSIBLE COPY
DRAFT

Recommendation #4: Monitoring and Enforcement

- FDA vs. NIH role
- Proposals to keep it simple
  - Objective definitions of scope
  - Use NCT #s and incorporate into “business processes”
  - Minimize “delay” provisions, and limit to public information
    - e.g., problems with “under review” by journal or FDA

Summary of Resource Implications

- Expand # trials in registry
  - Probably no significant increase in cost
- Add Structured Results database
  - ($10-20 million/year ??)
- Scientific Review (??)
- Monitoring and Enforcement (??)

Policies that would support registry efforts

- Incorporation of NCT # into all procedures
  - Facilitate use of FDA reviews
  - Aid in monitoring compliance
- Objective definition of scope
- NIH flexibility in definitions of data fields
- Avoid use of conclusions or narrative summaries for results

Thank You

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