NEUROSCIENCE TRIALS OF THE FUTURE: A WORKSHOP

Pragmatic Trials: Challenges and Opportunities for Neuroscience Trials

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Disclosure

- Full Time Employee of HealthCore, Inc, an Anthem subsidiary
- Shareholder of Anthem stock
- Presentation represents my views and not necessarily the views of my company

Key Pragmatic Trial Design Characteristics

- Designed to inform clinical and health policy decisions by evaluating the risks and benefits of health interventions in real world, community settings.
- Address practical questions about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice.
- Trials are prospective by design and include randomization but are still observational in nature.
- There is a growing demand for Pragmatic Trials from regulators, reimbursement and health technology assessment agencies, and from providers and patients.

Pragmatic Trials vs Randomized Controlled Trials

	Randomized Controlled Trial	vs	Pragmatic Trial
Tests if the Intervention Works Under	Ideal Circumstances		Real-World Circumstances
Conducted in	Controlled Setting		Usual Clinical Practice
Comparator	Placebo		Standard Care
Inclusion Criteria/ Patient Population	Extremely Restrictive		Minimally Restrictive
Treatment Regimen	Fixed and Protocol Driven		Flexible and Patient-Oriented
Goal	Regulatory Approval		Reimbursement Approval and Success in the Marketplace

Key Design Points for Implementing Pragmatic Studies

- Identifying a meaningful research question:
  - successful studies are those where the providers are invested in the results of the research because they believe it applies to their patient population
- Consider cluster randomization:
  - randomizing providers, practices or facilities to treatments rather than individual patients
- Reduce burden on provider by streamlining processes, minimizing unnecessary data capture, using Central IRB.
- Only capture essential safety data per FDA guidance for post-market studies.
- Understanding of real world treatment patterns to apply to research designs

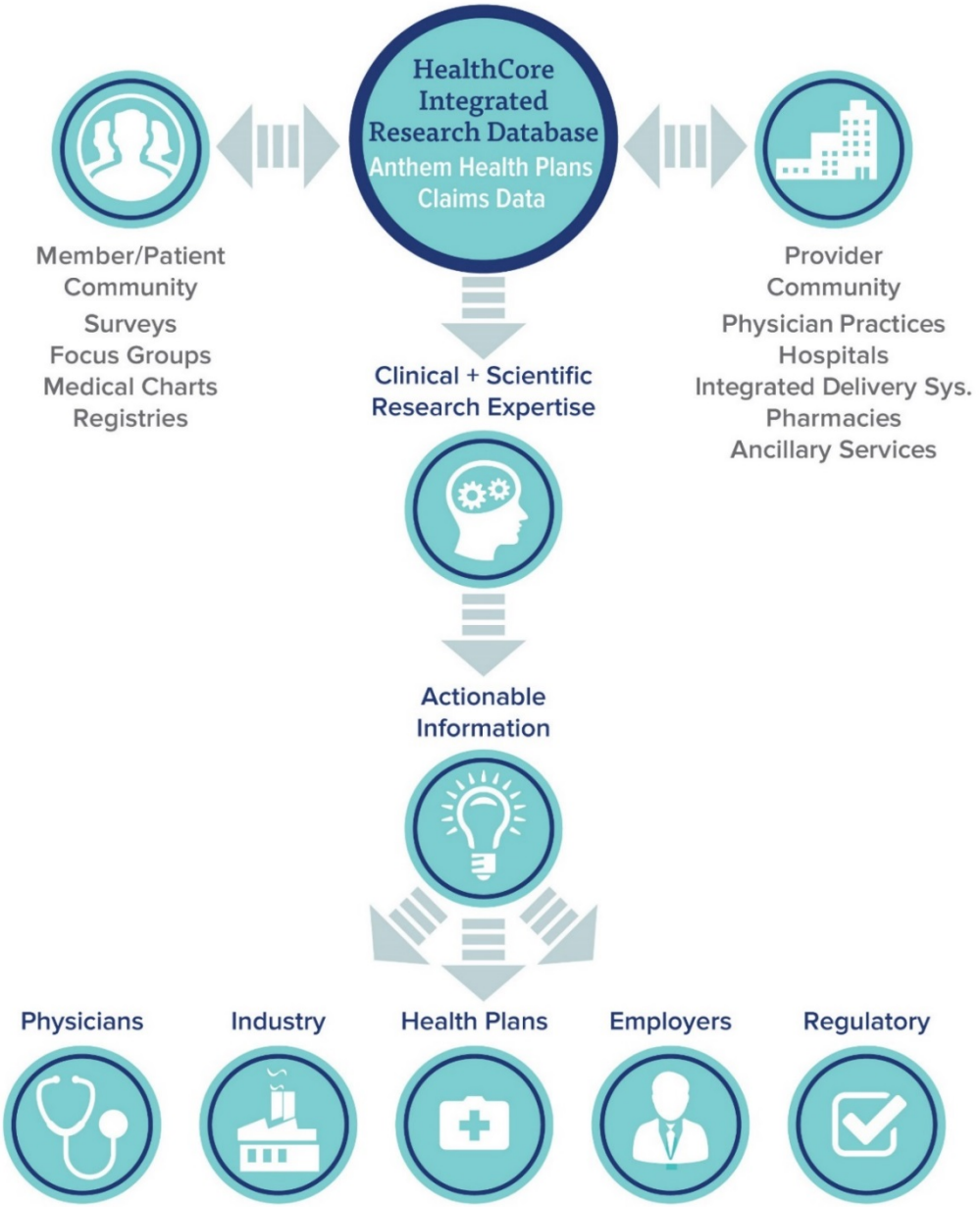
Cluster Randomization

- Cluster randomized studies are those where clusters of individuals rather than independent individuals are randomly allocated to treatment groups. In the Pragmatic trial setting this refers to randomizing physician practices to treatment groups rather than randomizing individual patients to treatments.
  - to avoid 'contamination' across interventions when trial participants are managed within the same setting (e.g., in a trial evaluating a dietary intervention, families rather than individuals may be randomized)
  - to reduce the burden on physician practices who might be research-naïve
  - to reflect real life healthcare delivery
- The use of cluster randomization does introduce a loss of statistical efficiency so cluster randomized studies require a larger sample size than patient randomized studies.

Meurer WJ, Lewis RJ. "Cluster Randomized Trials: Evaluating Treatments Applied to Group" JAMA 2015 **313**(20): 2068-2069

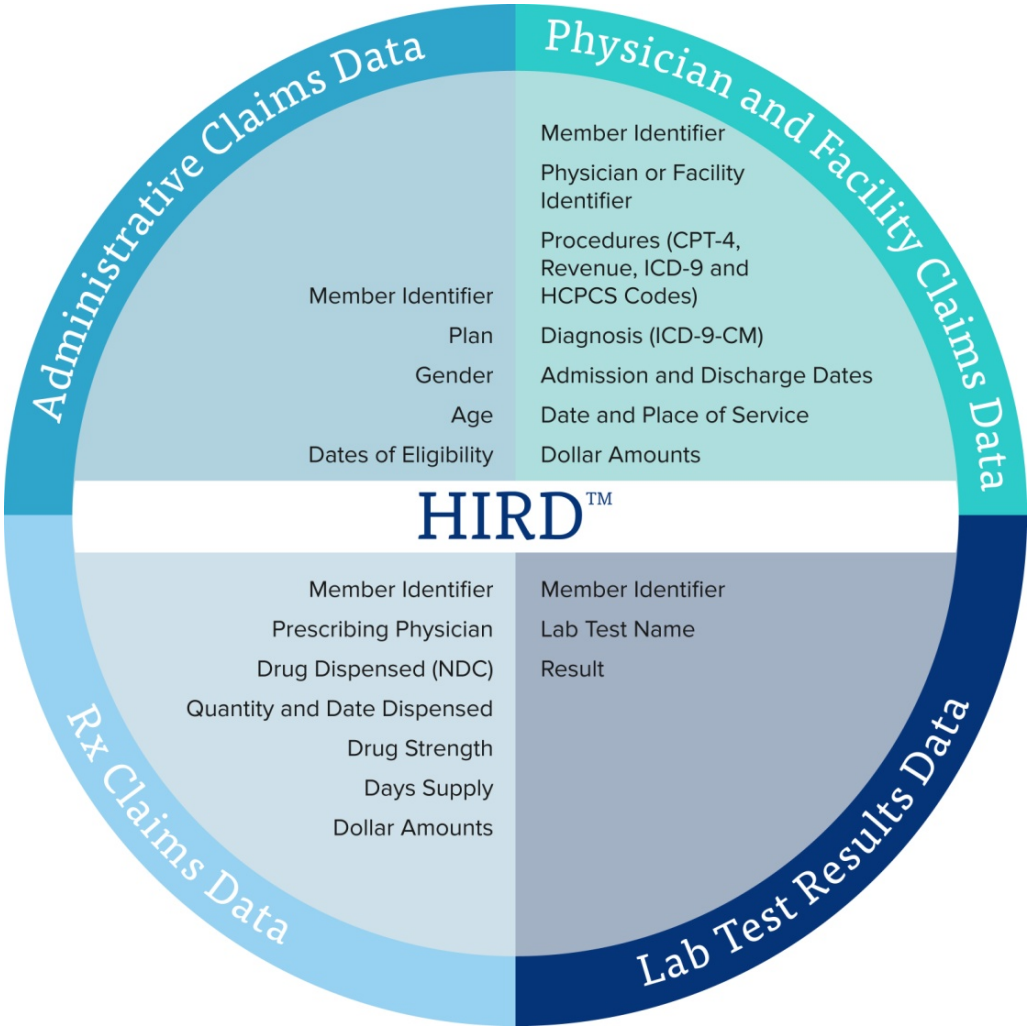
HIRE

HealthCore Integrated Research Environment

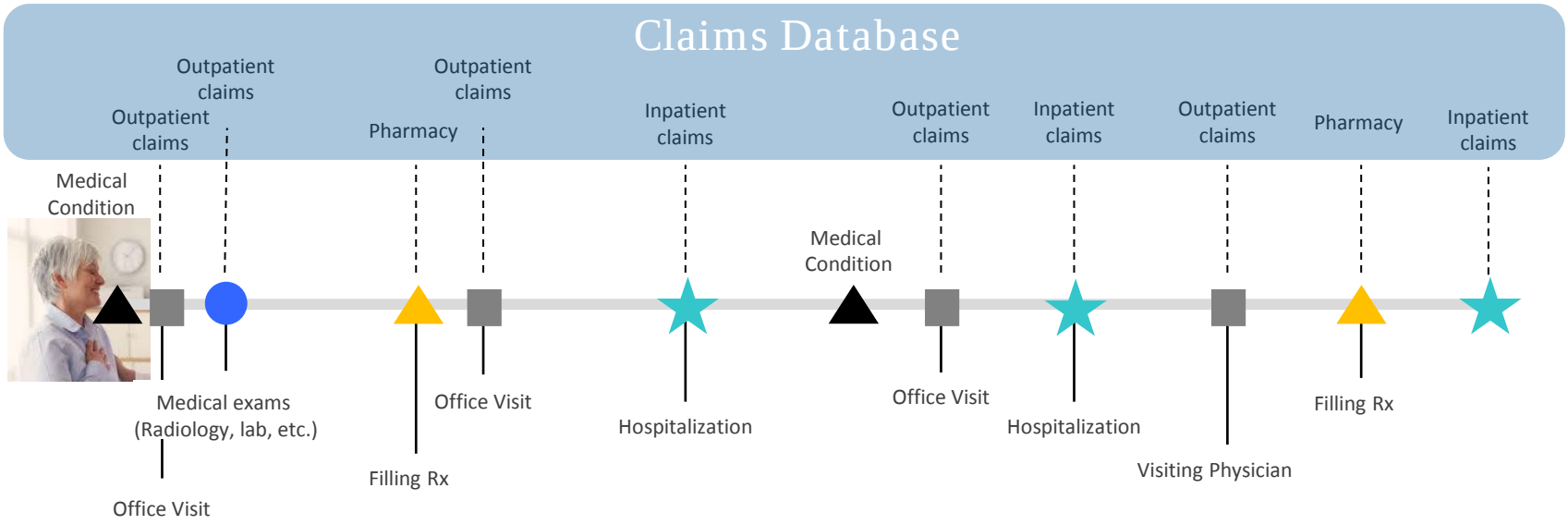


HIRD

HealthCore Integrated Research Database



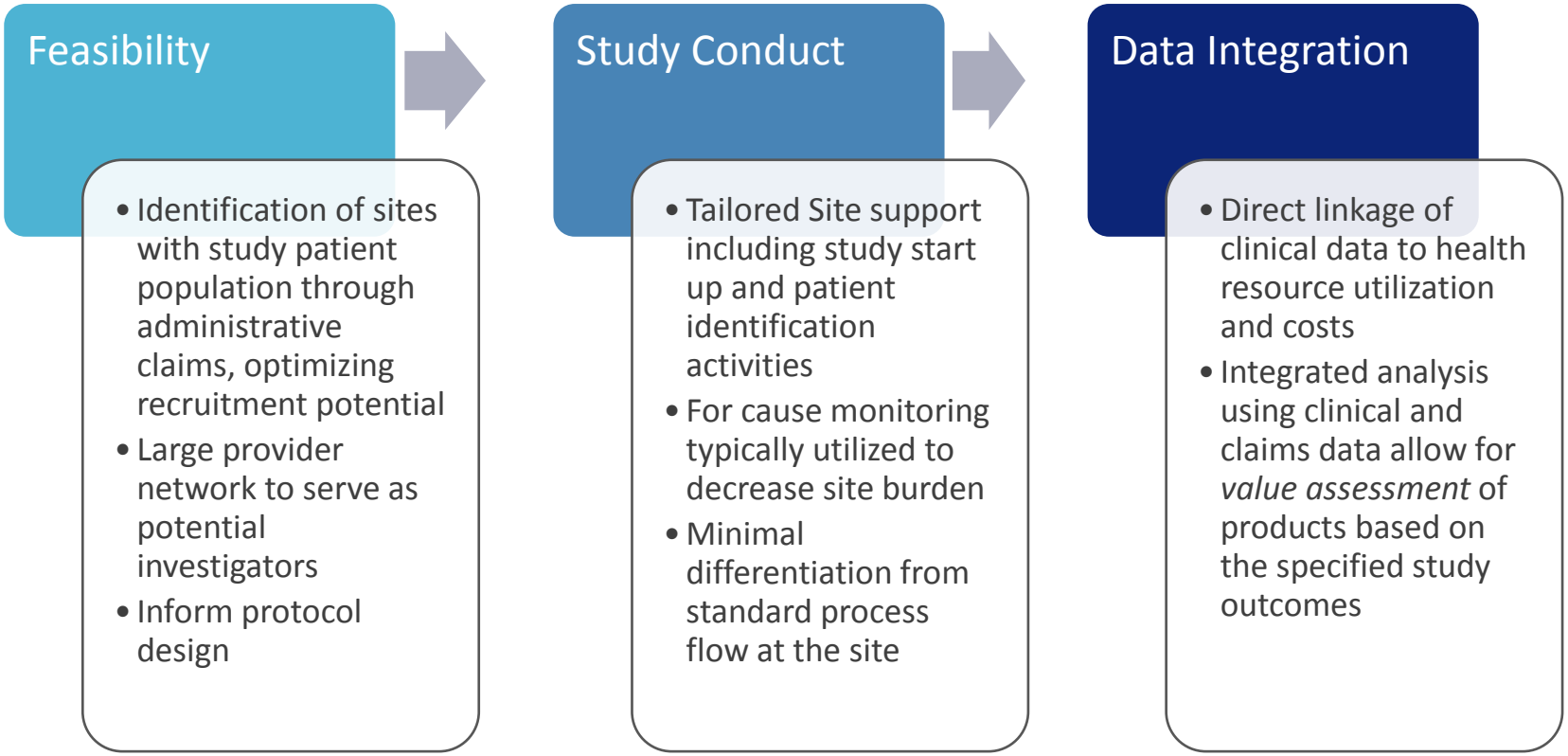
Utility of Claims Data for Longitudinal Follow-up



Data sources with complete claims capture on the individual provides:

- A very good overview of the patient's exposure to the healthcare system
- Good proxy(ies) for medical conditions and procedures performed
- Reasonable measure of clinical outcomes, though PPV is highly variable
- A good history of drug exposure and utilization
- Very good source for assessing healthcare costs, overall and segment

Key Steps to PCT Implementation



Pragmatic Studies in Neurosciences

Literature Search

- A systematic review of “practical clinical trials” was published in 2015* – key findings included:
  - PCTs in psychiatry evaluated mental health services or psychosocial interventions rather than specific pharmacotherapies
  - Of 157 PCTs in psychiatry, 30 (19%) were in psychopharmacology
- In a recent paper, Purgato discusses how trials have evolved in psychiatry and the concept of pragmatism is better understood with many excellent examples of pragmatic trials in psychiatry now available.**

*Vitiello, B. "Practical clinical trials in psychopharmacology: a systematic review." J Clin Psychopharmacol 2015 **35**(2): 178-183.
Purgato, M., et al. "Pragmatic design in randomized controlled trials." Psychol Med 2015 **45(2): 225-230.

Pragmatic Studies in Neurosciences

ClinicalTrials.gov

- Review of ClinicalTrials.gov showed numerous ongoing pragmatic trials in the neurosciences.
  - 367 studies are identified as Pragmatic trials or studies
    - ❖ 11% of these are in the Neurosciences
  - Although the studies are classified by the sponsor as Pragmatic, many also include RCT in the definition illustrating the ongoing confusion among many trial sponsors.
  - Most studies are comparing behavioral interventions and include cluster randomization (i.e. randomization of facilities or practices).
  - Other studies are comparing pharmaceuticals e.g. Pragmatic RCT Comparing Aripiprazole, Olanzapine and Haloperidol in the Treatment of Schizophrenia.

Conducting Pragmatic Trials in Neurosciences

Benefits	Challenges
Comparison of therapies and treatments for real-world outcomes	Real world outcomes in Neurosciences can be difficult to define
Cluster randomization - randomizing of facilities (nursing homes, in-patient facilities, physician practices) provides an effective design for comparing different therapies and an easier study to manage	Measuring adherence without impacting adherence – by asking a standard of care group about adherence will adherence be impacted.
Pragmatic trials with randomization provides a higher level of evidence than observational studies.	Patient population – challenging patient population for real-world studies (standard of care unclear, irregular physician visits, hospitalizations, low adherence and compliance to pharmaceuticals).


Q&A