Transformation II

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ARNOLD PALMER HOSPITAL
For Children
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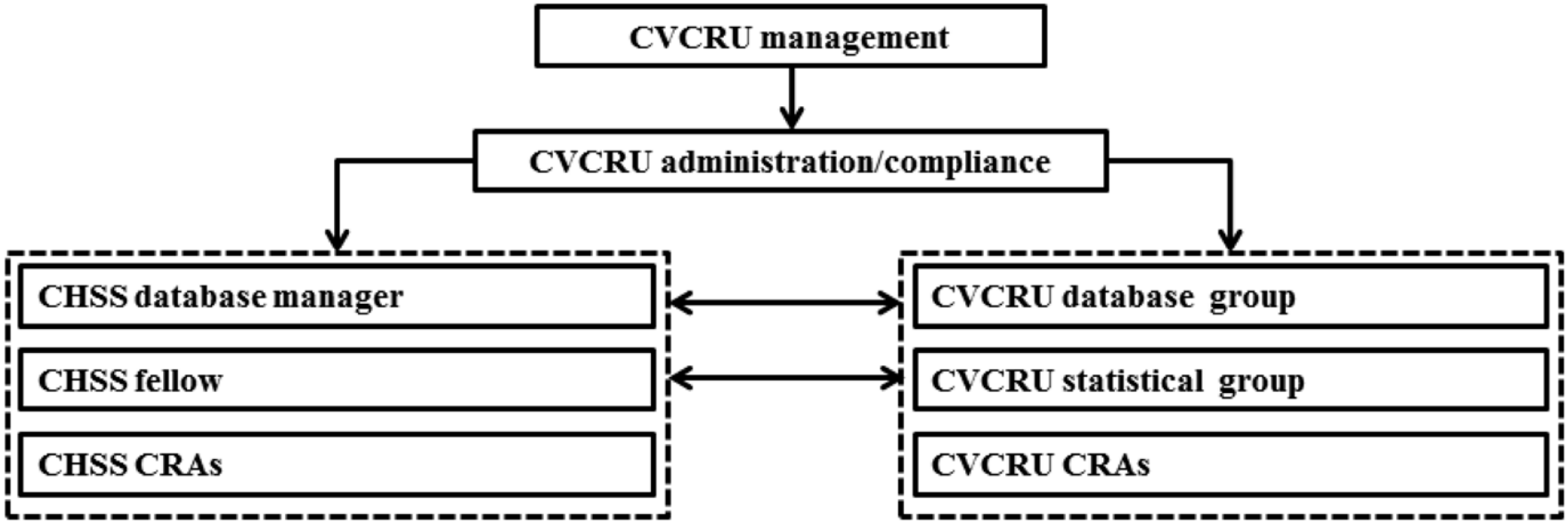
UNIVERSITY OF CENTRAL FLORIDA
College of Medicine

Challenges

- Burgeoning regulatory issues
- Data Center management
- Cost
- Enrollment participation
- Follow up
- Quality of data
- Impact of studies

Data Center Reorganization

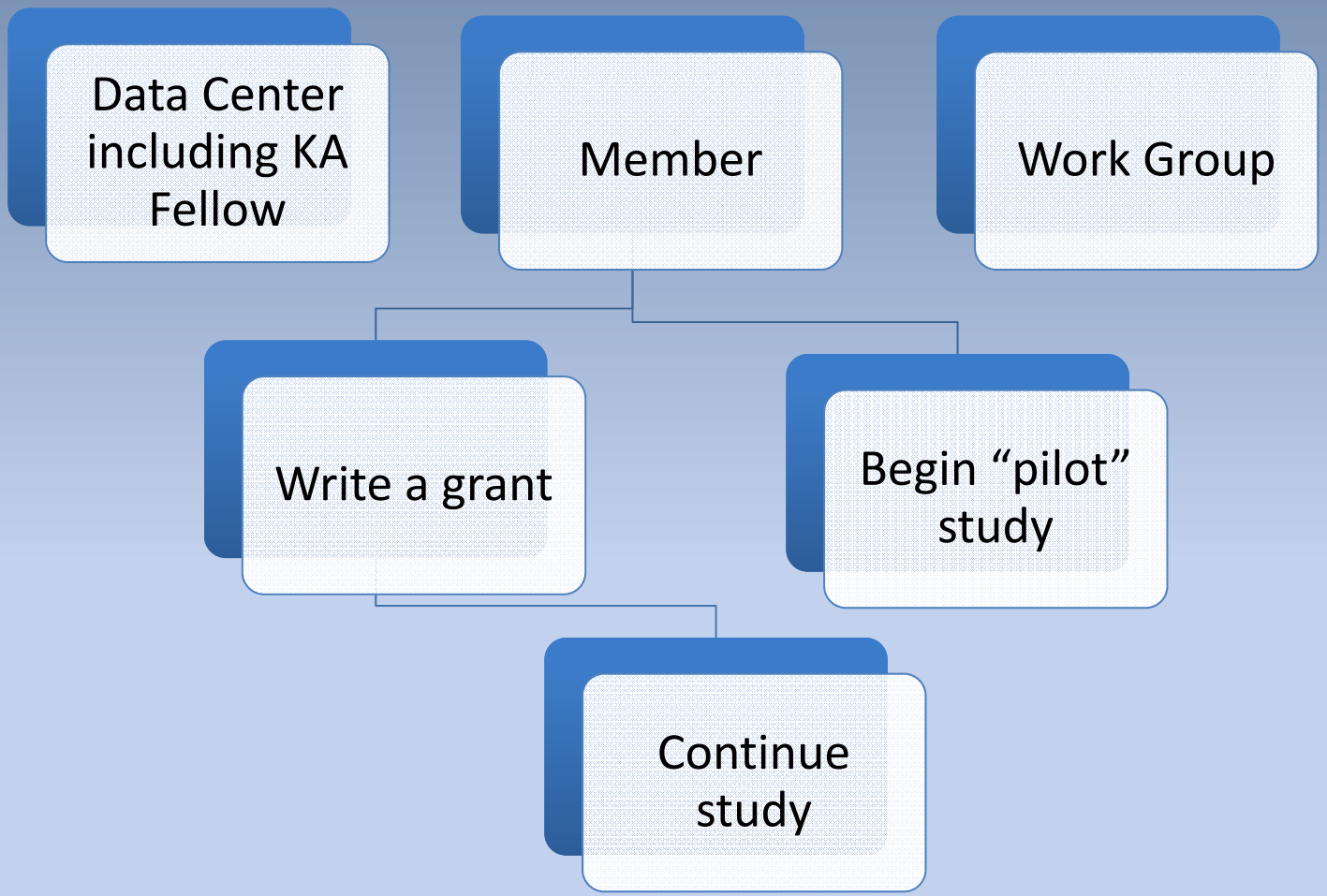


Data Center Reorganization

- Digitalize all DC patient records; store on online medium
- Move all databases to secure REDCap format
- Automate annual follow up using REDCap email client
- Evaluation and remodelling of DC staffing, organization and finances
- Move DC to Peter Gilgan Research & Learning tower

Creation of a study

Creation of a study



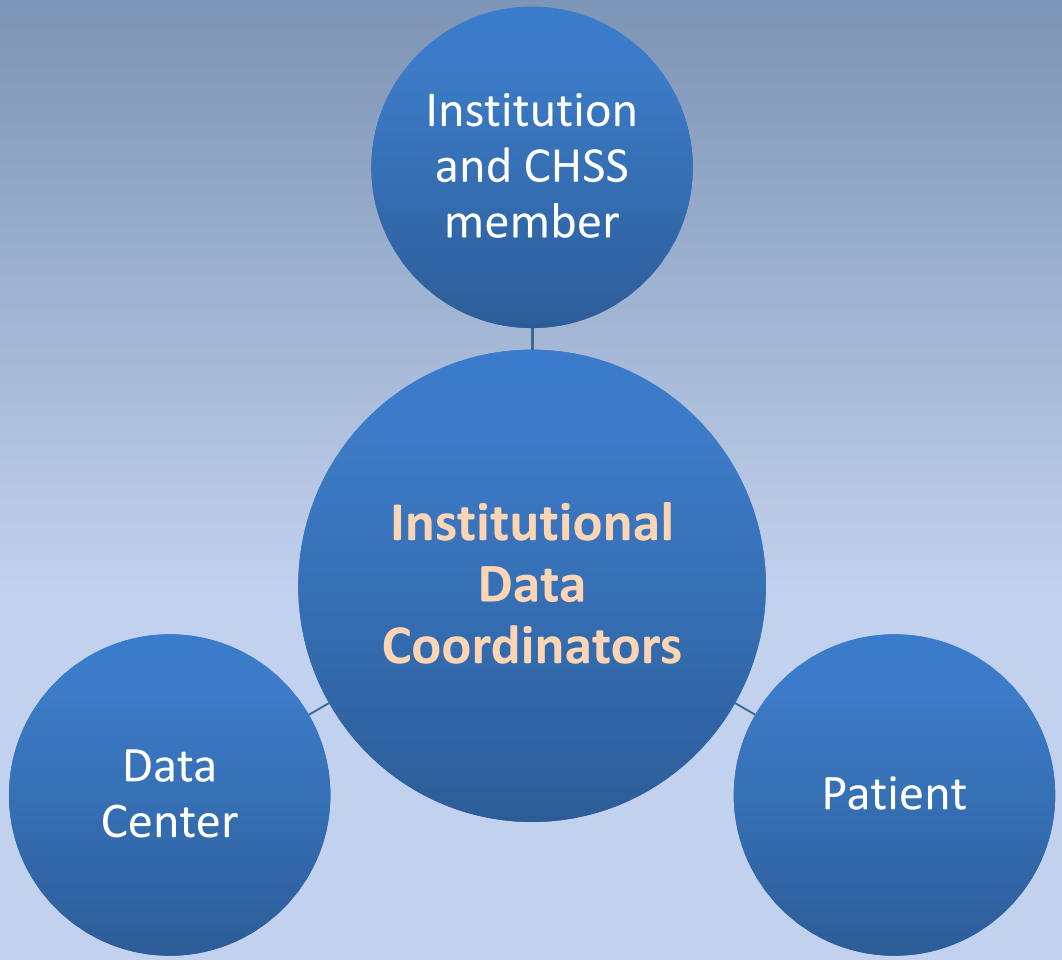
Encouraging Participation

- Should the members require every institution to enroll and follow up in order to remain CHSS member in good standing?
- Should we require all new members to attend Work Weekend?
- Should we require all new members to design a study and write a grant within first 3 years of membership?

Initiatives to improve follow up

- Conversion to e-mail
- Leveraging
  - Patients
  - Surgeons
  - Cardiologists
  - Institutional data coordinators
- Social media: Facebook

Institutional data coordinators



How many institutions have data coordinators that do not know about the CHSS Cohorts?

What if CHSS members "paired up" and wrote a CHSS-based grant every five years?

- 10 grants submitted per year
- If yield is 10%, that's 1 grant per year
- At average duration of 3 years, the DC would run continuously on 3 active grants

Data quality
and
Impact of studies

Are we meeting standards?

Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research

A Guidance Document for the Patient-Centered Outcomes Research Institute

Gilklich R, Dreyer N, Leavv M, Velentgas P, Khurana L

www.pcori.org

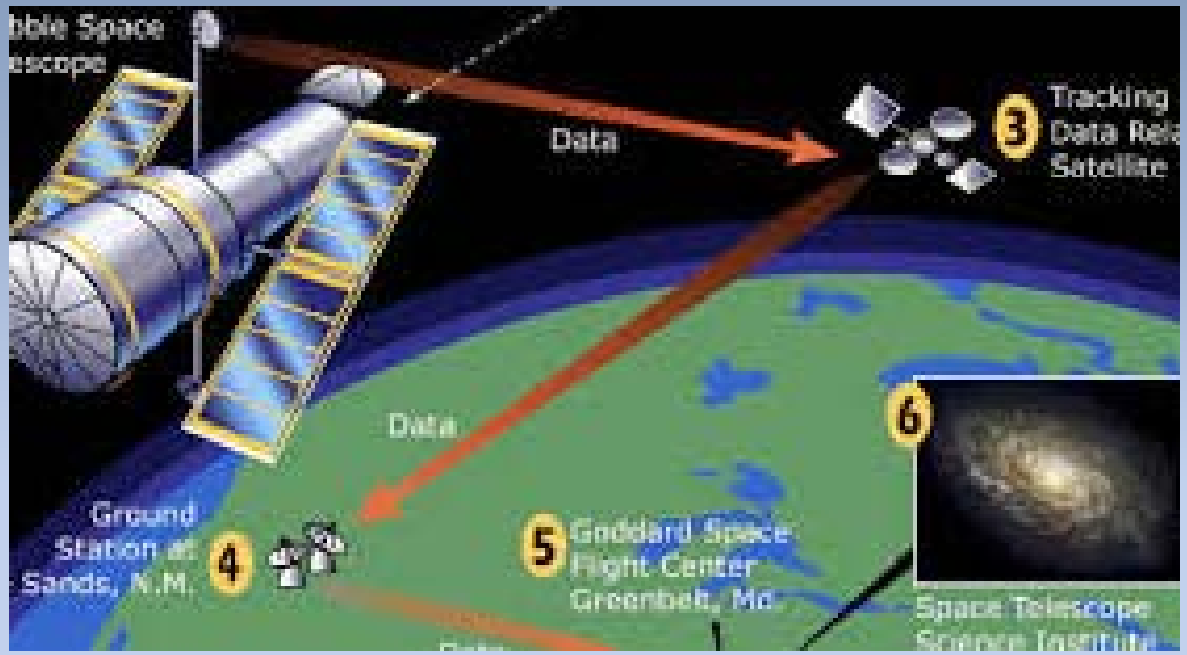
www.outcome.com

March, 2012

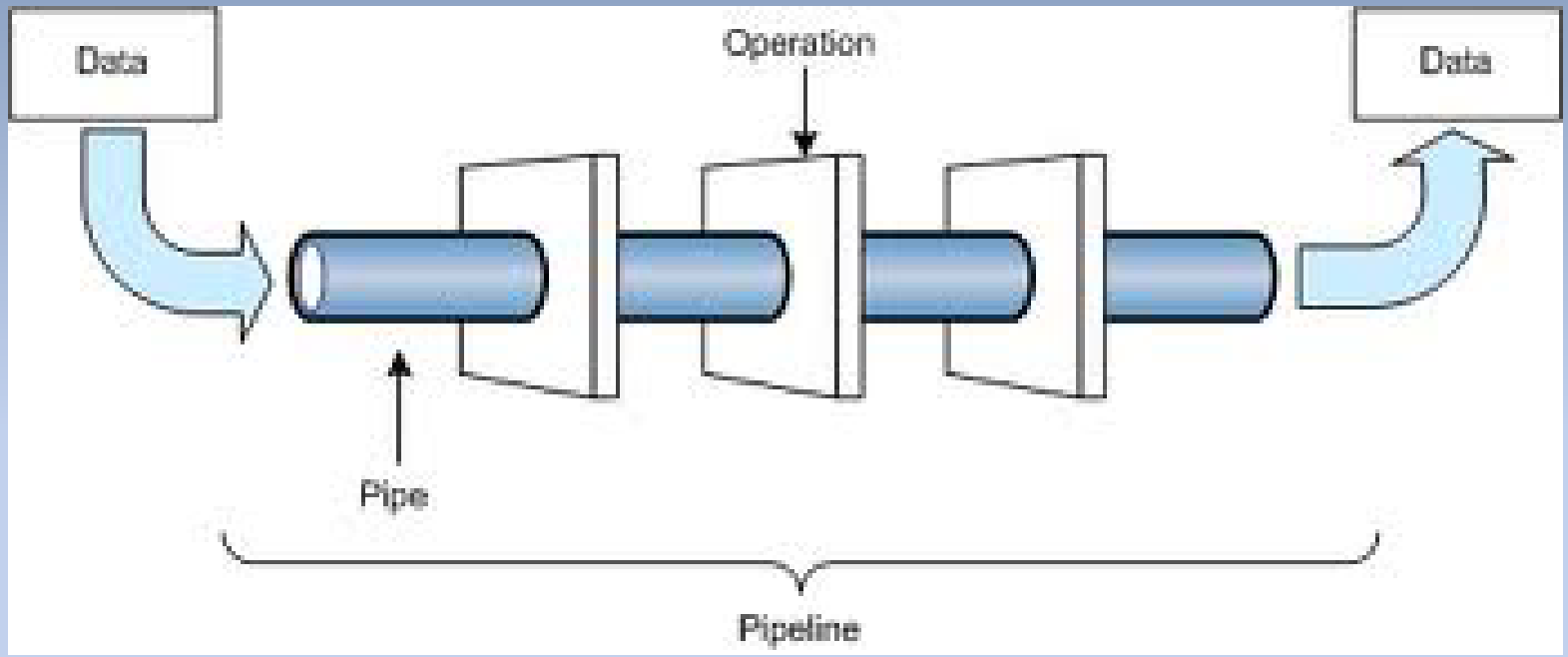
The Future: Leverage the data

- Structure the cohorts so we can perform studies with high quality hybrid design
- Cohort and study design that conserves costs
- Collaborations
- Data sharing; database merging
- Data flow: pipelines

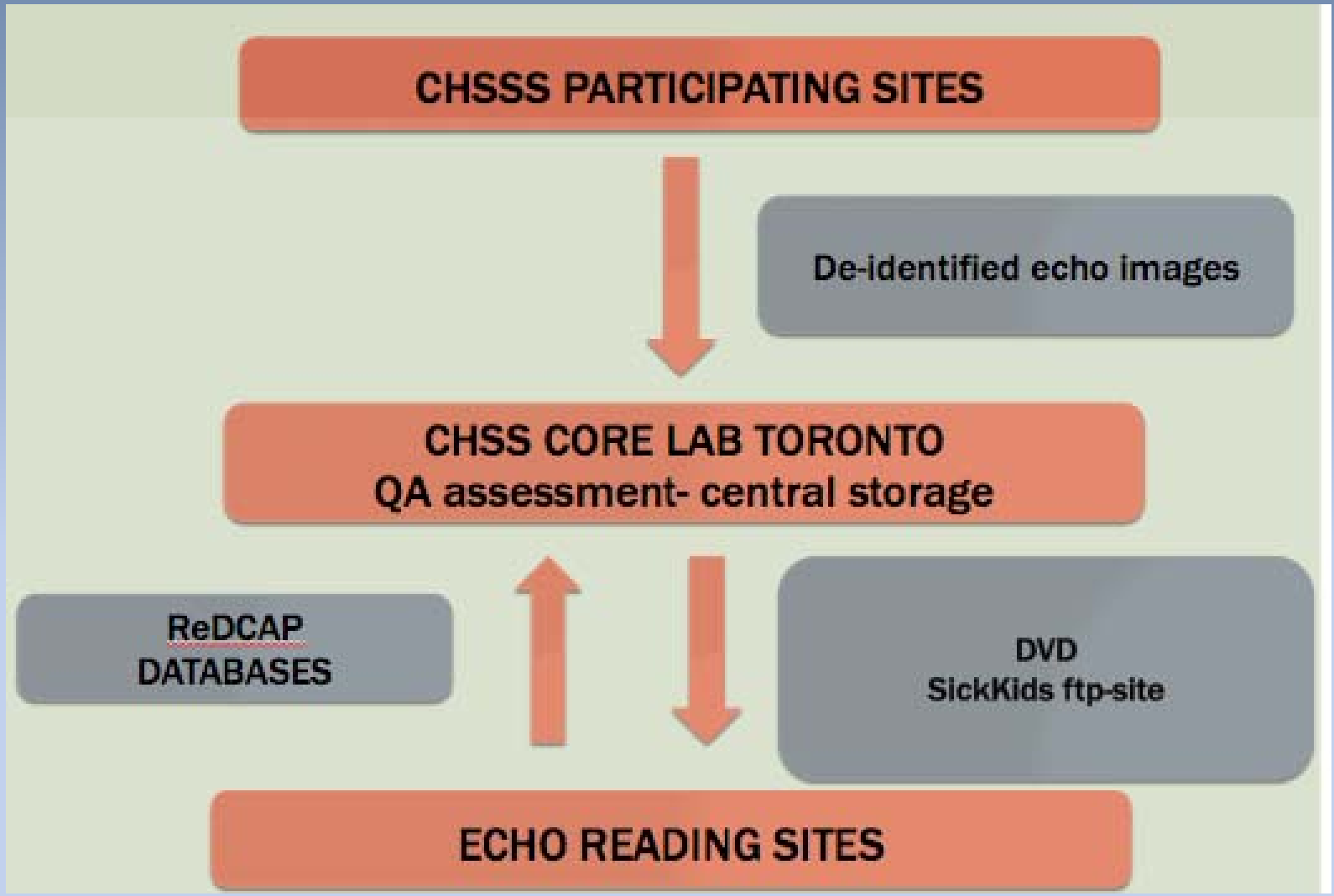
Data Pipeline



Data Pipeline



Imaging Core Lab



Approaches to Study Design

- Non-linear mixed model regression
- Regression discontinuity design
- Hybrid designs: “trial within a registry”
- Basket, umbrella and master designs
- “Optimal design” theory
- “Value of Information” analysis

Collaborative Registries and Studies CHSS and ???

- Single institution:
  - CHOP, AAOCA, Cohen, Brothers
  - Cleveland Clinic, AA FHS/transition to care, Stackhouse
- Other organizations
  - STS Congenital Database
  - ECHSA
  - PHN
- Registry of Biobanks (Gruber)
- Multi-national collaboratives (Genetics; Leducq; Gruber)

END

Regression discontinuity design

- In statistics, econometrics, political science, epidemiology, and related disciplines, a **regression discontinuity design (RDD)** is a quasi-experimental pretest-posttest design that elicits the causal effects of interventions by assigning a cutoff or threshold above or below which an intervention is assigned. By comparing observations lying closely on either side of the threshold, it is possible to estimate the local Average treatment effect in environments in which randomization was unfeasible.

Umbrella Trial

- In an “umbrella trial,” patients with a given type of cancer are assigned a specific treatment arm based on the molecular makeup of their cancer. Umbrella trials have many different arms under the umbrella of a single trial. Patients are assigned to an arm on the trial based on the molecular makeup of their cancer. Umbrella trials allow us to test a variety of targeted drugs at the same time in the patients who are most likely to benefit, i.e. those with cancers that have the specific molecular abnormality targeted by the drug.

Master Protocols

- Our current system for providing administrative and regulatory oversight of clinical trials was designed before umbrellas, buckets and master protocols were being considered. It was designed when most clinical trials involved testing a given treatment in a given cancer type at a single institution. Every clinical trial available at a given institution was only made available to patients after it was reviewed by an institutional committee responsible for assuring the trial was scientifically strong and another committee that assured protection of patient rights.
- With the new trial designs, even the largest cancer centers will likely enroll only 1 or 2 patients onto many arms of a study. Putting each arm of each study through the scientific and ethics committees of each institution separately, as we have done for decades, would require a huge and duplicative administrative effort that, in this era of shrinking resources, would prevent such studies from being successful. What is needed is a new approach to administration, oversight and regulation of clinical cancer trials that is more efficient yet still assures safety and protection of patient rights. This requires reassessing the value of long standing policies, and working together more effectively, not only in conducting clinical cancer trials, but also in administering and overseeing them.

Optimal design theory

- In the design of experiments, **optimal designs** are a class of experimental designs that are optimal with respect to some statistical criterion. The creation of this field of statistics has been credited to Danish statistician Kirstine Smith.[2][3]
- In the design of experiments for estimating statistical models, **optimal designs** allow parameters to be estimated without bias and with minimum-variance. A non-optimal design requires a greater number of experimental runs to estimate the parameters with the same precision as an optimal design. In practical terms, optimal experiments can reduce the costs of experimentation.

Optimal design theory

- Optimal designs offer three advantages over suboptimal experimental designs:[5]
- Optimal designs reduce the costs of experimentation by allowing statistical models to be estimated with fewer experimental runs.
- Optimal designs can accommodate multiple types of factors, such as process, mixture, and discrete factors.
- Designs can be optimized when the design-space is constrained, for example, when the mathematical process-space contains factor-settings that are practically infeasible (e.g. due to safety concerns).

Value of information analysis

- VOI is an approach to research prioritization which uses Bayesian methods to estimate the potential benefits of gathering further information (through more research) before making a decision. In “classic” decision analysis, the optimal choice between two or more strategies is the one with the highest expected value; for each strategy, the expected value is calculated by multiplying the probability of a given outcome by the value of that outcome. Because this calculation is almost always an estimate made on the basis of imprecise or incomplete data, the result is more properly referred to as the *expected value given current information*. The underlying uncertainty in the data raises the possibility that a decision made on the basis of the expected value given current information may be incorrect. Using Bayesian methods, it is possible to calculate the *expected value given perfect information*—in other words, the outcome if the optimal decision were made every time. The difference between these two values is the *expected value of perfect information* (EVPI)

Basket Trial

- Instead of starting with multiple clinical trials in different diseases (which requires duplication of regulatory and infrastructure efforts), we start with one trial — the basket — and one or more targets, and allow patients with multiple diseases to enroll in cohorts or groups.
- If one group shows good response, we expand this group to immediately assess whether others could benefit from the new therapy. If another group is unfortunately not showing evidence of effectiveness, this group may be closed and the patients can move on to consider other therapy.

1. Develop a formal study protocol. Develop a formal study protocol specifying: at least one purpose of the registry (e.g., effectiveness, safety, natural history of disease, quality improvement, or other) and research question(s); objectives; study design; target population, including subgroups of interest (if applicable); exposures of interest; primary and secondary endpoints; data sources and linkage plans, if any; measure(s) of effect; sample size and statistical power (if applicable); use of any standardized data dictionaries (nationally or internationally accepted); and likely sources of bias and plans to address them.

2. A priori, specify plans for data analysis that correspond to major aims. Describe the analytic approaches that will be used to address the major research aims. Provide definitions of key exposures, endpoints, and covariates. Identify patient subgroups of interest, plans (if any) for how new subgroups of interest will be identified, and/or how analysis plans may be adapted based on changing needs and scientific advances. Specify plans for how missing data will be handled.

3. Choose outcomes that are clinically meaningful, patient-centered, and relevant to decision- makers. Identify and select outcomes that are clinically meaningful, patient-centered, and relevant to decision-makers. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of “clinically meaningful,” “patient- centered,” and “relevant to decision-makers,” such as patient and decision-maker input from meetings or surveys or published literature relevant to the question of interest.

4. Describe data linkage plans, if applicable. For studies involving linkage of registry data to another data source, describe the other data source and its appropriateness and limitations for addressing specific hypotheses. Consider any additional requirements that may influence successful linkage, such as information needed to match patients, selection of data elements, and definitions used.

5. Plan follow-up based on the registry objective(s). The objective(s) of the registry should determine the type, extent, and length of patient follow-up. Ensure that the follow-up time planned is adequate to address the main objective and that patient retention efforts planned are suitable to the target population and anticipate challenges to retaining patients in the study. Expected loss to follow-up and potential impact on the results, including possible biases resulting from differential loss to follow-up, should be described.

6. Use validated scales and tests. Validated scales and tests should be used when such tools exist for the purpose needed.

7. Address the potential for re-identification, if applicable, when using previously collected data. Studies that use previously collected data (e.g., studies involving linkage of data or using repurposed data) that have the potential for re-identification must address this issue in accordance with local, national, and international regulations.

8. When using previously collected data, address the impact of the legal and privacy conditions under which the data were collected initially. Registries that re-use data must assess the legal and patient privacy conditions under which the data were originally collected and address the impact of those conditions on the new study.

9. Take appropriate steps to ensure data quality. Employ data checks using range and consistency checks where applicable. Create a quality assurance plan that addresses data review and verification. A risk-based approach to quality assurance is advisable.

10. Document and explain any modifications to the protocol. Modifications to a registry protocol may be necessary for a variety of reasons. When modifications are necessary, they should be clearly documented and justified.

11. Collect data consistently. Provide clear, operational definitions of data elements. Create and distribute standard instructions to data collectors. Use standardized data element definitions and/or data dictionaries whenever possible.

12. Enroll and follow patients systematically. Enroll patients systematically and follow them in as unbiased a manner as possible, using similar procedures at all participating sites. Describe how patients and providers were recruited into the study to allow the impact of selection bias to be clearly understood and any efforts employed to confirm the quality of adherence to agreed-on enrollment practices.

13. Monitor and minimize loss to follow-up. Monitor loss to follow-up to ensure that follow-up is sufficiently complete for the main objective. Devote reasonable efforts to minimizing loss to follow-up. Describe the impact of actual loss to follow-up on the study results, including possible biases resulting from differential loss to follow-up.

14. Use appropriate statistical techniques to address confounding. For registries that are intended to evaluate the effectiveness or safety of interventions, use appropriate statistical techniques to address confounding.

15. Use sensitivity analyses to determine the impact of major decisions. For registries that are intended to evaluate the effectiveness or safety of interventions, use sensitivity analyses to determine the impact of key assumptions, such as exposure and outcome definitions, on the research questions.

16. Assess and report the extent of missing data. For primary and secondary data collection, assess and report the extent of missing data at key points of follow-up for data elements that are critical to addressing the primary study questions.

17. Provide sufficient information in reports of the registry findings to allow for assessments of the study's internal and external validity. Describe the following elements in the registry report, if applicable: methods, including selection of study participants, data collection activities, settings where data were collected, analytic techniques, and approaches to handling missing data; data quality activities, including any issues that may have affected the quality or integrity of the data; comparability of the registry participants to the target population and any efforts to minimize selection bias; extent of missing data for key exposures, risk factors, and outcomes and impact of missing data on key study questions; length of follow-up period and impact of loss to follow-up on key study questions; and the role and impact of potential confounders.