Advisory Panel on Rare Disease Summer 2014 Webinar

August 13, 2014

Patient-Centered Outcomes Research Institute

Welcome

Bryan Luce, PhD, MBA
Chief Science Officer, PCORI

Patient-Centered Outcomes Research Institute

Agenda

2:00 – 2:05 PM: Welcome	B. Luce
2:05 – 2:20 PM: Update on Leadership Meeting	M. Summar/V. D. Gaizo
2:20 – 2:35 PM: Registry Projects Updates	S. Wahba/J. R. Teagarden/ Y. R. Rubinstein
2:35 – 2:50 PM: PCORI's Topic Generation and Research Prioritization Process	B. Luce/K. O. Walker
2:50 – 3:20 PM: PCORI's Merit Review Process	T. Tafari
3:20 – 3:30 PM: Rare Disease Submitted Topics	G. Martin
3:30 – 3:40 PM: Rare Disease Cross-Cutting Issues	N. Aronson
3:40 – 3:55 PM: CER Topics	D. Hickam
3:55 – 4:50 PM: Outreach and Other Solutions	G. Martin
4:50 – 5:00 PM: Recap and Next Steps	B. Luce/M. Summar/V. D. Gaizo
5:00 PM: Adjourn	

Update on Leadership Meetings

Marshall L. Summar, MD
Chair, Advisory Panel on Rare Disease, PCORI
Vincent Del Gaizo
Co-Chair, Advisory Panel on Rare Disease, PCORI

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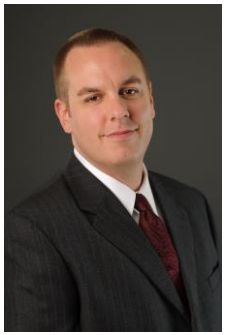
Members of the leadership team

Bryan Luce, PhD, MBA
Chief Science Officer

David Hickam, MD, MPH
Program Director, Clinical Effectiveness Research

Lia Hotchkiss, MPH
Program Director, Eugene Washington PCORI Engagement Awards



Greg Martin
Deputy Director of Stakeholder Engagement

Naomi Aronson, PhD
Methodology Committee

Marshall L. Summar, MD
Chair, Advisory Panel on Rare Disease

Vincent Del Gaizo
Co-Chair, Advisory Panel on Rare Disease

Leadership Priorities for the RDAP

- Analyze PCORI processes for conduciveness to rare disease research:
  - Topic generation
  - Research prioritization
  - Merit review
  - Outreach
- Help identify priority rare disease topics
- Commission a landscape review on standards for rare disease research
- Evaluate PCORI's rare disease portfolio

Additional Leadership Action Items

- Appointment of Naomi Aronson, PhD (Methodology Committee member) as ex-officio member
- Agenda setting

What can the RDAP do?

- Advise on drafting education materials to explain what CER is in layman's terms
- Market/create a forum where patients know where to go to submit and learn
- Engage the rare disease community

Registry Projects Updates

PCORnet: Sarita Wahba, MSPH, MS
Program Officer, CER Methods and Infrastructure, PCORI
NORD: J. Russell Teagarden, DMH, MA
Advisory Panel on Rare Disease, PCORI
GRDR: Yaffa R. Rubinstein, MS, PhD
Advisory Panel on Rare Disease, PCORI

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Rare PPRNs Update

Sarita Wahba, MSPH, MS

Program Officer, CER Methods and Infrastructure, PCORI

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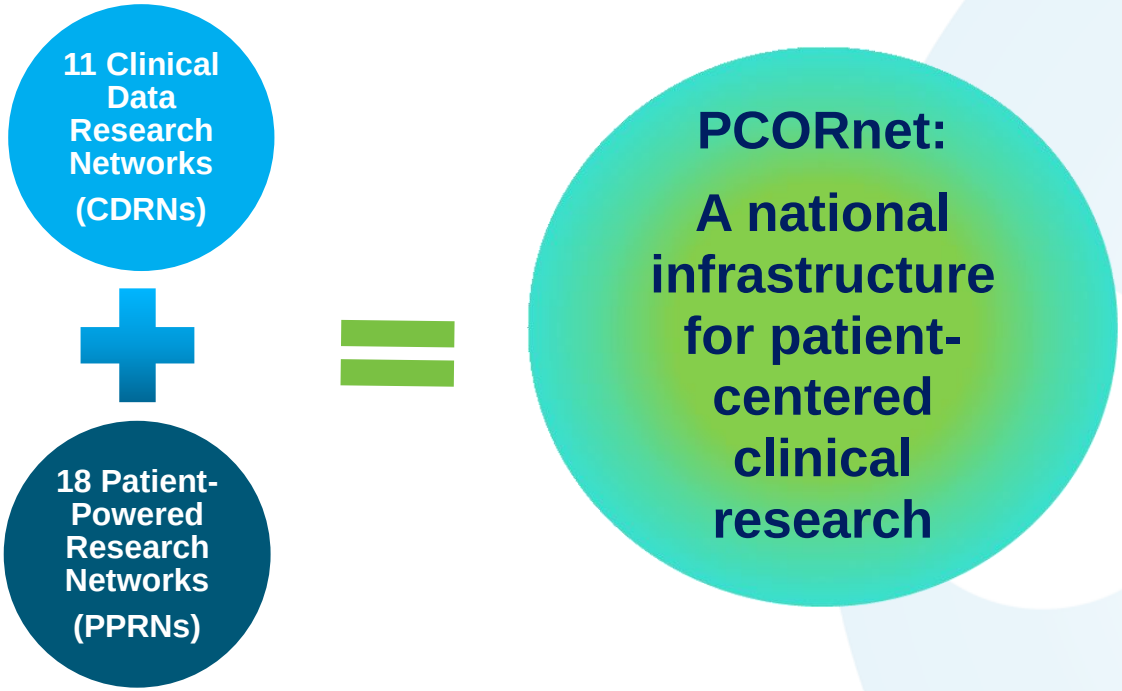
PCORnet's goal

PCORnet seeks to improve the nation's capacity to conduct clinical research by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.

PCORnet embodies a “community of research” by uniting systems, patients & clinicians



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Goals for each Patient-Powered Research Network (PPRN)

- Establish an activated patient population with a condition of interest (Size >50 patients for rare diseases; >50,000 for common conditions)
- Collect patient-reported data for ≥80% of patients in the network
- Involve patients in network governance
- Create standardized database suitable for sharing with other network members that can be used to respond to “queries” (ideas for possible research studies)

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What are the Rare Dx PPRNs doing?

- Developing individual network and PCORnet policy documents
- Outreach and enrollment
- Building out databases / portals / mobile apps
- Developing and updating surveys
- Developing patient-friendly informed consents
- Mapping to the PCORnet CDM
- Developing and testing computable phenotypes
- Building relationships with other networks

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Progress update on key domains

- **Types of Data Being Collected**:
  - demographic 9/9
  - vital signs 6/9 (1/9 undecided)
  - enrollment, diagnosis data, and encounter data: 8/9 ((1/9 undecided)
- **Patient portals**: 9/9
  - Launched and enrolling patients: 2/9
- **IRB Approval:**
  - Full: 3/9
  - Partial: 4/9
  - Under Review: 1/9
  - Not submitted yet: 1/9
- **Governance Structures Developed:** 9/9
- **Patient Engagement**: 9/9 with patients in governance

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Challenges / concerns

- Patient retention
- Increasing diversity
- Outreach to clinicians
- Need training materials and resources to support the development of patient representatives
- Lack of structured data elements and well defined computable phenotypes for rare diseases

Rare Disease PPRNs

Network Name
ALD Connect
Community-Engaged Network for All (CENA)
DuchenneConnect Patient-Report Registry Infrastructure Project
NephCure Kidney Network for Patients with Nephrotic Syndrome
Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium
Phelan-McDermid Syndrome Data Network
PI Patient Research Connection: PI-CONNECT
Rare Epilepsy Network (REN)
Vasculitis Patient Powered Research Network

NORD Registry Project Update

J. Russell Teagarden, DMH, MA
Advisory Panel on Rare Disease, PCORI

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NIH/NCATS GRDR℠ Program: Global Rare Diseases Patient Registry Data Repository

Yaffa Rubinstein Ph.D.
Program Director for Patient Resources
for Clinical and translational Research
Office Of Rare Diseases, NCATS

PCORnet RDAP Summer Webinar
August 13, 2014

GRDR℠ Data Repository

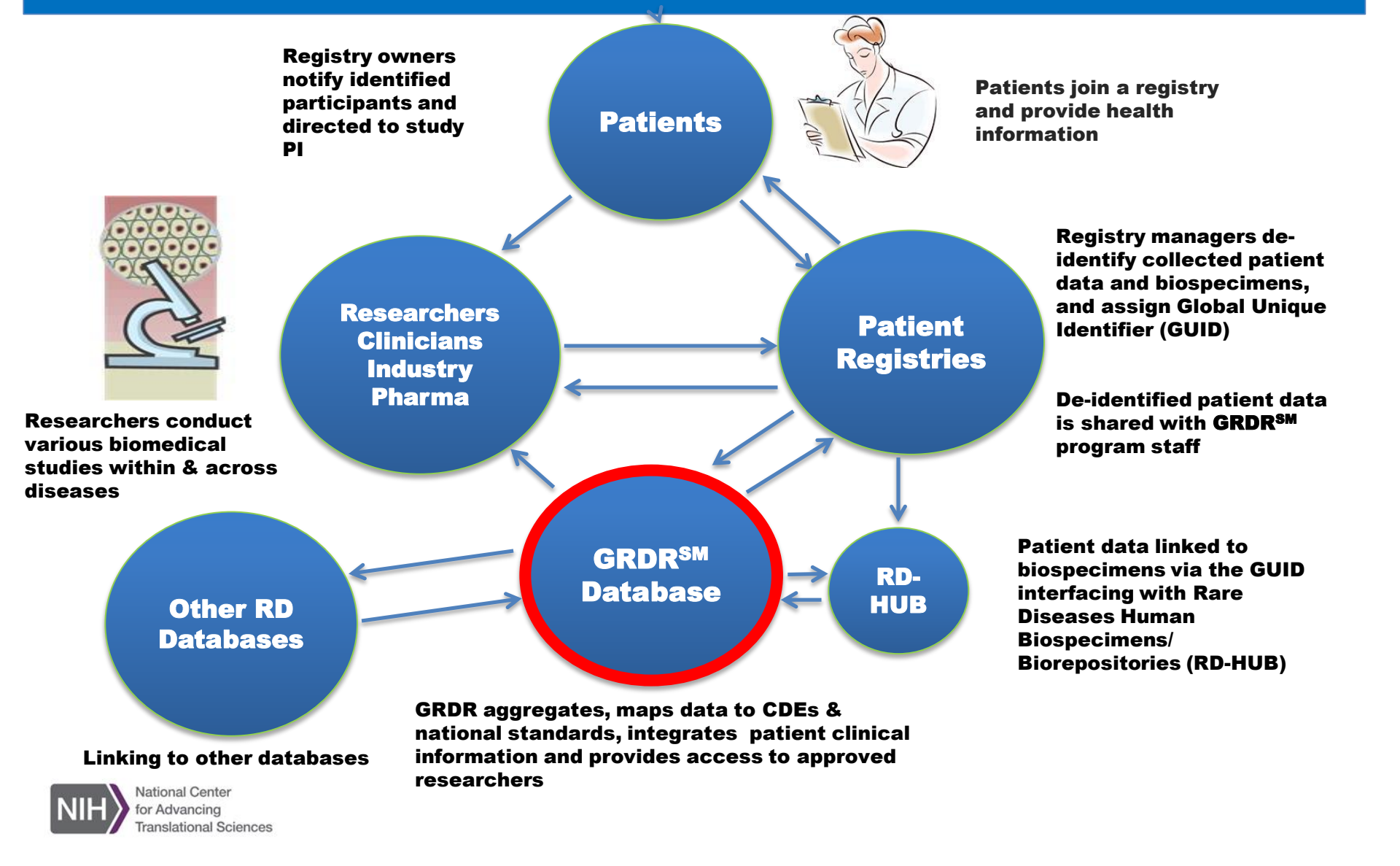
https://grdr.ncats.nih.gov/

The NIH/NCATS Global Rare Diseases Patient Registry Data Repository/GRDR℠ program is designed to advance research for rare diseases and, through application of scientific insights gained, to further research for common diseases as well.

The aim is to develop a Web-based resource that aggregates, secures and stores de-identified patient information from many different registries for rare diseases, all in one place. The ultimate goal is to improve therapeutic development and quality of life for the many millions of people suffering with a rare disease.

NIH/NCATS GRDR℠ Program

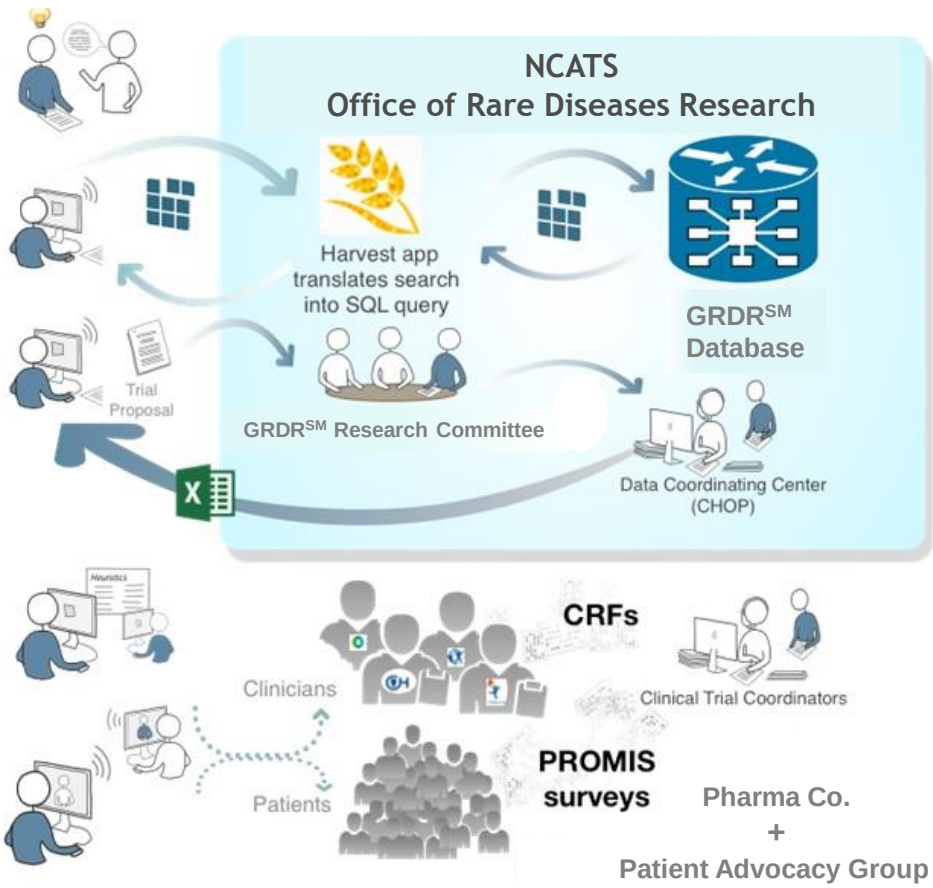
Global Rare Diseases Patient Registry Data Repository



NIH National Center for Advancing Translational Sciences

Example: Planned Program Workflow

- Dr. Smith wonders whether a **side effect** of a new drug ("X"), which was developed to treat another disease, might **treat symptoms** of his patient with a rare disease.
- Dr. Smith logs into the **secure GRDR[SM] access portal.** He searches for all patients on ***drug X*** and finds **150 patients across 7 registries**.
- Dr. Smith then **proposes a study** to the GRDR[SM] Research Committee to analyze overlap between his patients and others taking ***drug X***.
- After **approval,** GRDR[SM] Data Coordinating Center staff **send Dr. Smith a data file** customized to his needs.
- Dr. Smith receives **funding** from the pharmaceutical company that makes ***drug X*** to initiate a clinical trial of ***drug X*** in his rare disease patients, **based on his initial analysis.**
- Dr. Smith, the pharmaceutical company and related patient advocacy group collaborate to **conduct a clinical trial** of ***drug X*** in his patients.



GRDR[SM] Program Collaboration

Through its GRDR[SM] program, NCATS staff currently are working in collaboration with a team from the Children's Hospital of Philadelphia to create a standardized and interoperable data repository.

The repository is being developed with an open-science principle that supports clinical research, population health, and improvements in health care for patients with rare diseases.

Resources Developed/Provided through The NIH/NCATS GRDR℠ Program

- Common Data Elements (CDEs)
- Template Informed Consent
- Central IRB Services
- Access to Global Unique Identifier (GUID)
- Mapping patients' data to CDEs and national Standards
- Ability to link patient data to their biospecimens through the Rare Diseases Human Biospecimens/Biorepositories (RD-HUB)
- Website with information for rare disease community and investigators with a link to other resources

NIH/NCATS GRDR[SM] Program Value

- ***For patients and their families***: Increase awareness for their specific rare disease
- ***For rare disease organizations***: Map data from each registry to standards facilitating interoperability among them and between other databases
- ***For investigators and industry:*** Facilitate research collaboration and cross-disease analyses by lowering barriers to data access

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Related Publications

- The case for a global rare-diseases registry. *Lancet*. 2011;377(9771):1057-9.
- Patient registry for the overlooked patient. *Contemp Clin Trials*. 2010;31(5):393.
- Letter to the editor. *Contemp Clin Trials*. 2010;31(5):393.
- Creating a global rare disease patient registry linked to a rare diseases biorepository database: Rare Disease-HUB (RD-HUB). *Contemp Clin Trials*. 2010;31(5):394-404.
- Informed consent process for patient participation in rare disease registries linked to biorepositories. *Contemp Clin Trials*. 2012;33(1):5-11.
- Informed consent template for patient participation in rare disease registries linked to biorepositories. *Rare Dis Orphan Drug*. 2012;1(2):69-74.
- Rare Diseases Human Biospecimens/Biorepositories (RD-HUB). http://biospecimens.ordr.info.nih.gov/

For more information contact Yaffa.Rubinstein@nih.gov
301-402-4338

PCORI's Topic Generation and Research Prioritization Process

Bryan Luce, PhD, MBA
Chief Science Officer, PCORI
Kara Odom Walker, MD, MPH, MSHS
Deputy Chief Science Officer, PCORI

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Topic Generation and Research Prioritization Overview

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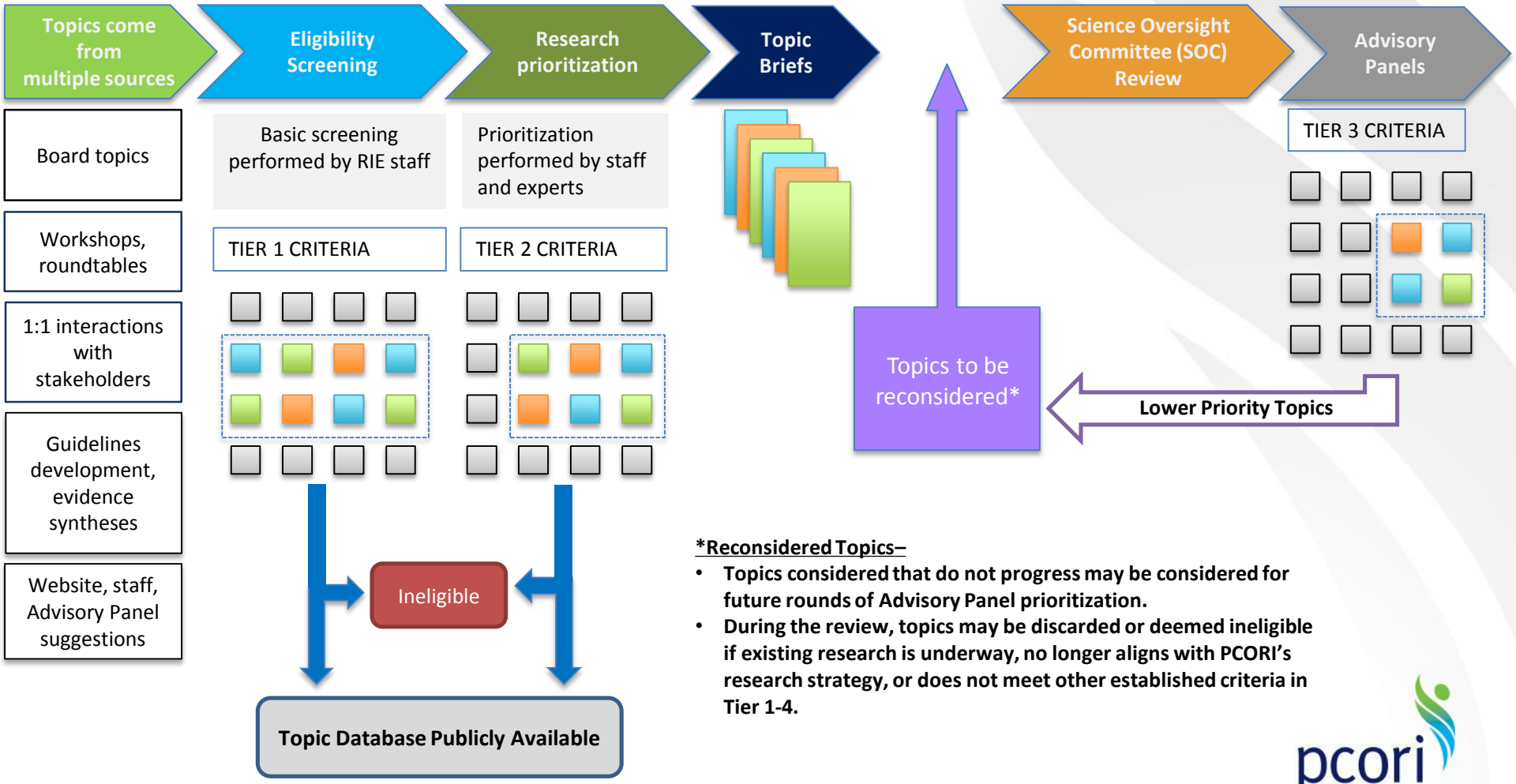
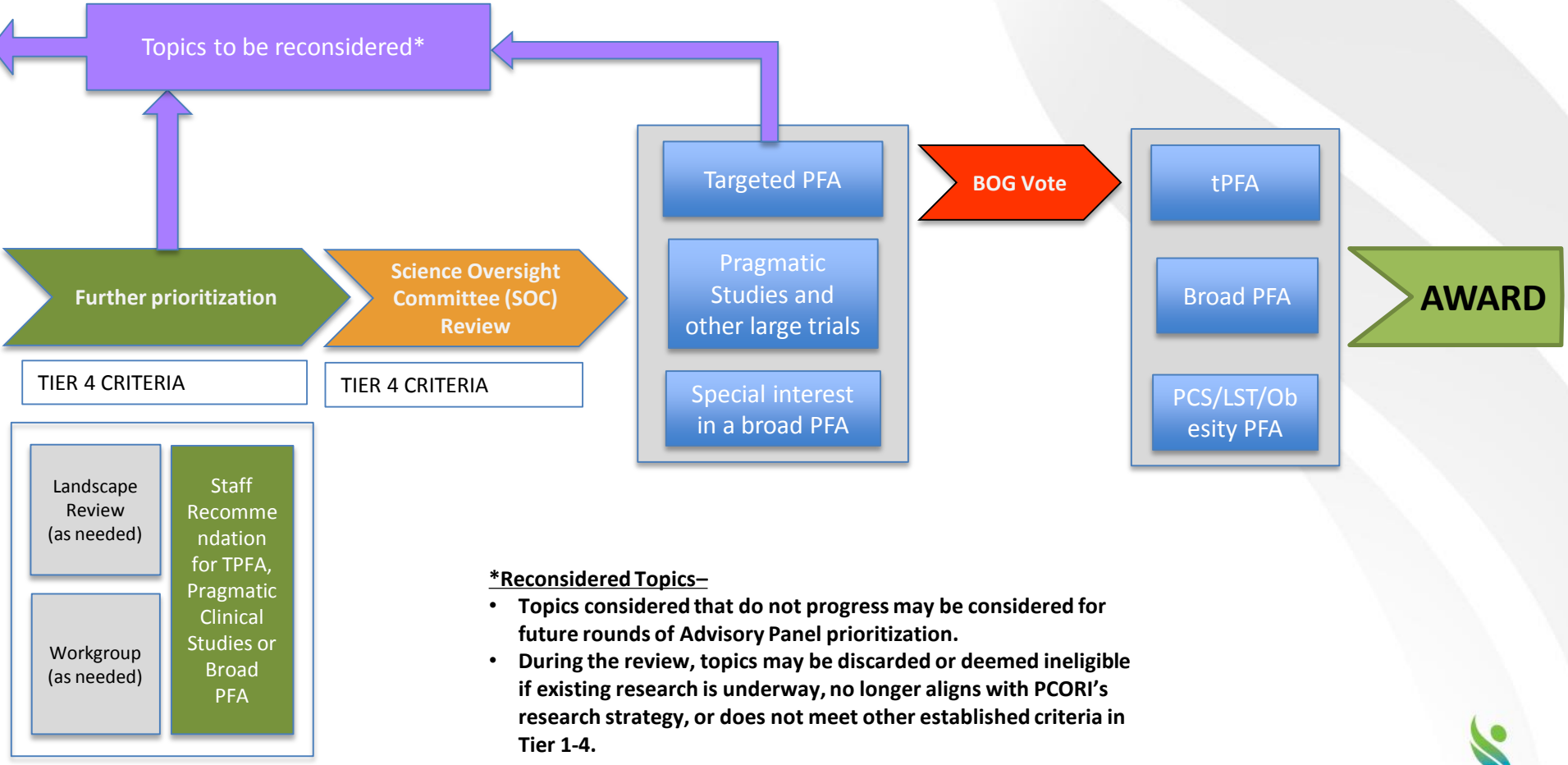
Topic Generation and Research Prioritization (1/2)



***Reconsidered Topics–**

- **Topics considered that do not progress may be considered for future rounds of Advisory Panel prioritization.**
- **During the review, topics may be discarded or deemed ineligible if existing research is underway, no longer aligns with PCORI's research strategy, or does not meet other established criteria in Tier 1-4.**

Topic Generation and Research Prioritization (2/2)



***Reconsidered Topics–**

- **Topics considered that do not progress may be considered for future rounds of Advisory Panel prioritization.**
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Tier 1 Criteria: Determine Eligibility

(Initial Screen by Staff)

- Is this a **comparative effectiveness research** question?
  - Are two or more options (one of which can be usual care) being compared? *Eligible*
  - Or is it instead a comment, a descriptive question, or a question of disease causation or biological mechanism. *Ineligible*
- Is this question **duplicative with another question** already in the research topic database? *Ineligible*
- Is the question **patient-centered**: i.e., is the comparison relevant to patients, their caregivers, clinicians or other key stakeholders and are the outcomes relevant to patients? *Eligible*

Tier 2 Criteria: Screening By Program Staff

[Each criterion is scored from 1 (low) – 5 (high)]

- Impact of the condition on the health of individuals and populations
- Important evidence gap is believed to exist *(e.g., by virtue of a recent, credible evidence synthesis)*
- Is PCORI-funded research likely to close this evidence gap?
- Likelihood of implementation of relevant findings into practice (e.g., do one or more major stakeholder groups endorse the question)

Tier 3: Advisory Panel Criteria

(Applied by Advisory Panels after reviewing topic briefs)

- **Patient-Centeredness:** Is the comparison relevant to patients, their caregivers, clinicians or other key stakeholders and are the outcomes relevant to patients?
- **Impact of the Condition on the Health of Individuals and Populations:** Is the condition or disease associated with a significant burden in the US population, in terms of disease prevalence, costs to society, loss of productivity or individual suffering?
- **Assessment of Current Options:** Does the topic reflect an important evidence gap related to current options that is not being addressed by ongoing research?
- **Likelihood of Implementation in Practice:** Would new information generated by research be likely to have an impact in practice? (e.g., Does one or more major stakeholder groups endorse the question?)
- **Durability of Information:** Would new information on this topic remain current for several years, or would it be rendered obsolete quickly by new technologies or subsequent studies?

Tier 4: Targeted PFA Criteria

(*Distinguishing topics for targeted PFAs from topics for Pragmatic Clinical Studies list*)

- **A specific question (comparison)** has been identified about prevention, diagnostic, treatment options or system-level interventions that are currently covered in at least some settings.
- **The importance of the topic** as determined by high scores from the advisory panel, strong interest from one or preferably more than one key stakeholder groups, and strong assessment of potential to change practice, warrants set aside funding and closer involvement in the study by PCORI.
- **May require higher level of funding than the usual pragmatic clinical study** – either for larger sample size, longer follow-up or more complex interventions/data collection needed to pursue the specific question.

PCORI's Merit Review Process

Tsahai Tafari, PhD

Senior Program Officer, Merit Review, PCORI

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PCORI Merit Review

The goal of PCORI Merit Review is to identify applications that have the strongest potential to improve patient outcomes.

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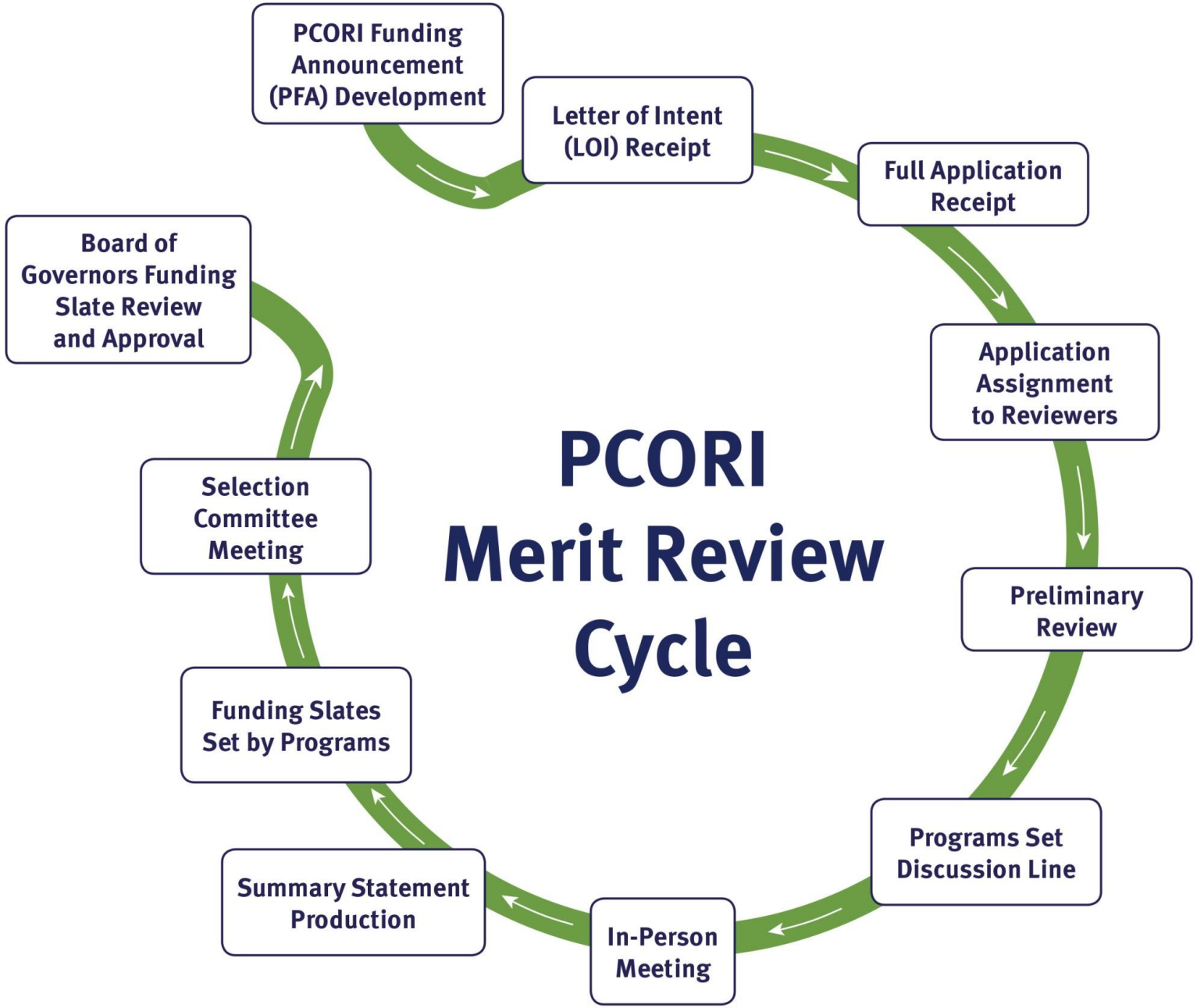
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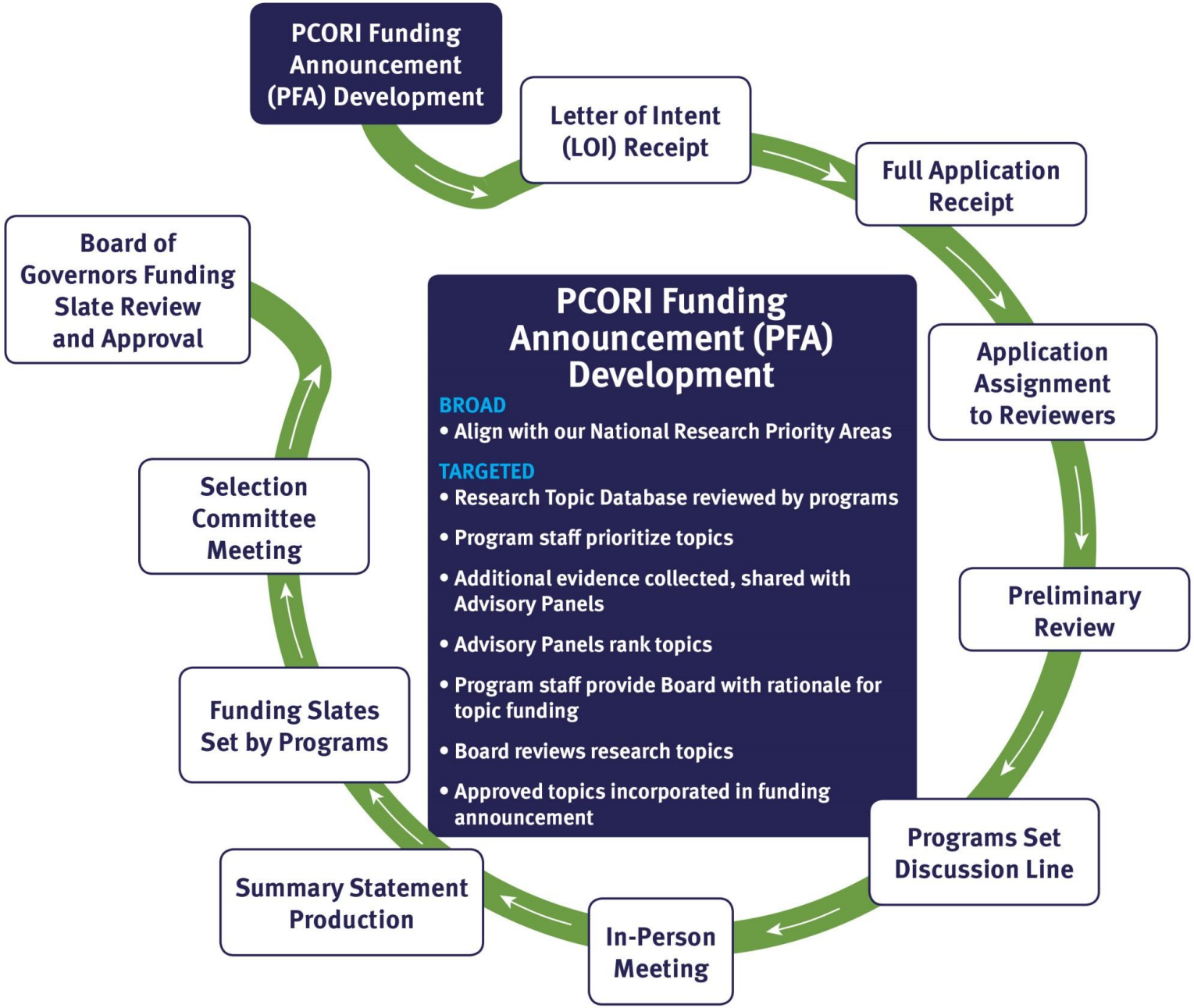
PCORI Merit Review Cycle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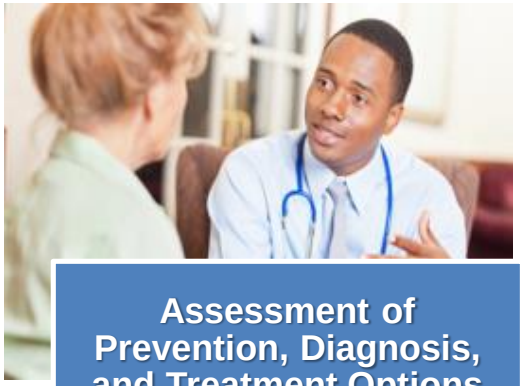
PCORI Funding Announcement (PFA) Development
BROAD
• Align with our National Research Priority Areas
TARGETED
• Research Topic Database reviewed by programs
• Program staff prioritize topics
• Additional evidence collected, shared with Advisory Panels
• Advisory Panels rank topics
• Program staff provide Board with rationale for topic funding
• Board reviews research topics
• Approved topics incorporated in funding announcement

Our National Priorities for Research



Assessment of Prevention, Diagnosis, and Treatment Options

Improving Healthcare Systems

Communication & Dissemination Research

Addressing Disparities

Accelerating PCOR and Methodological Research

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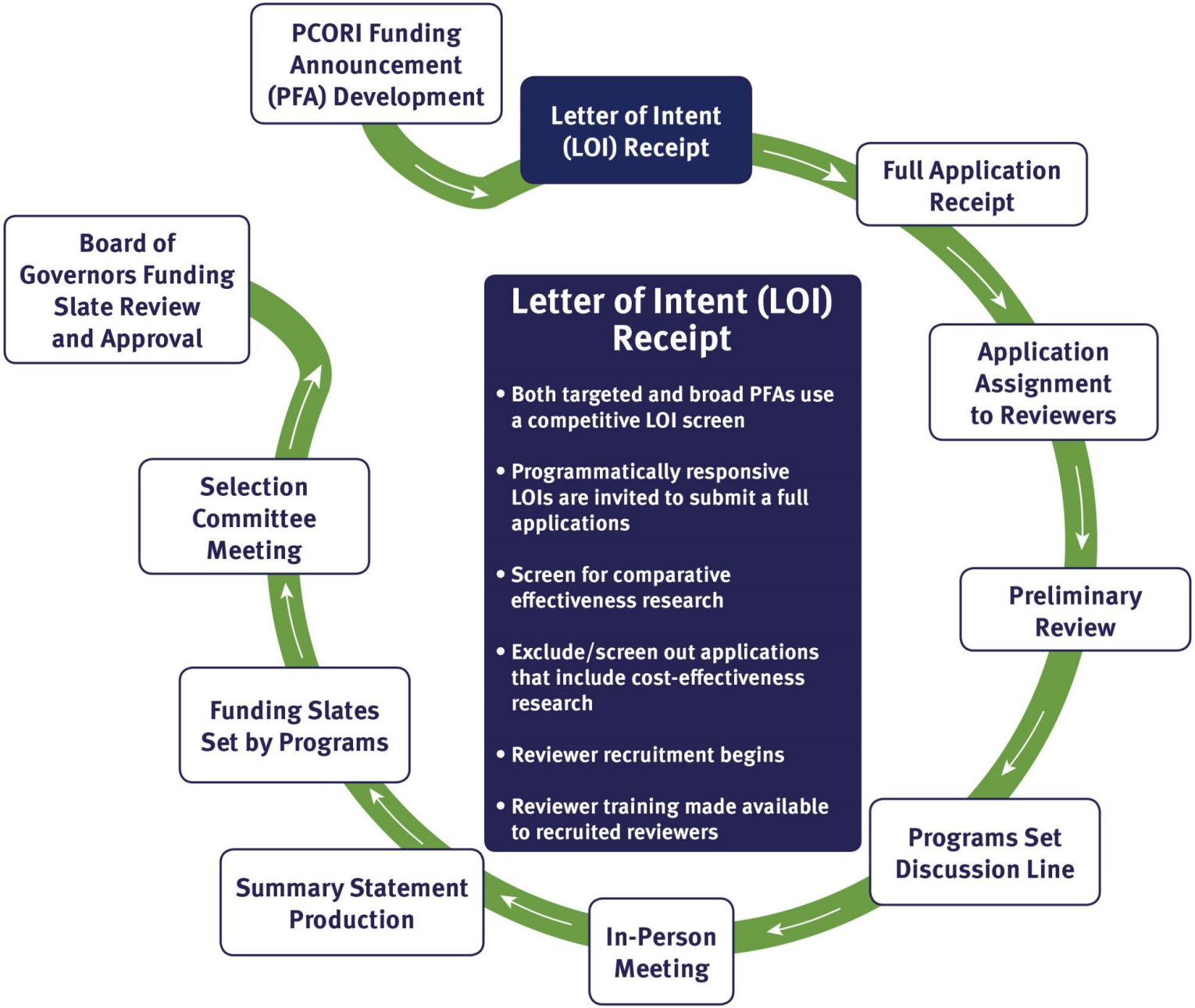
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Letter of Intent (LOI) Receipt
• Both targeted and broad PFAs use a competitive LOI screen
• Programmatically responsive LOIs are invited to submit a full applications
• Screen for comparative effectiveness research
• Exclude/screen out applications that include cost-effectiveness research
• Reviewer recruitment begins
• Reviewer training made available to recruited reviewers

Responsiveness Review

- Letters of intent are reviewed based on criteria detailed in each PFA
- Additional screening for
  - Comparative effectiveness research
  - Exclusion of cost-effectiveness analysis
- Only responsive LOIs will be invited to submit a full application
- Based on the topic areas of the received LOIs, reviewer recruitment will begin

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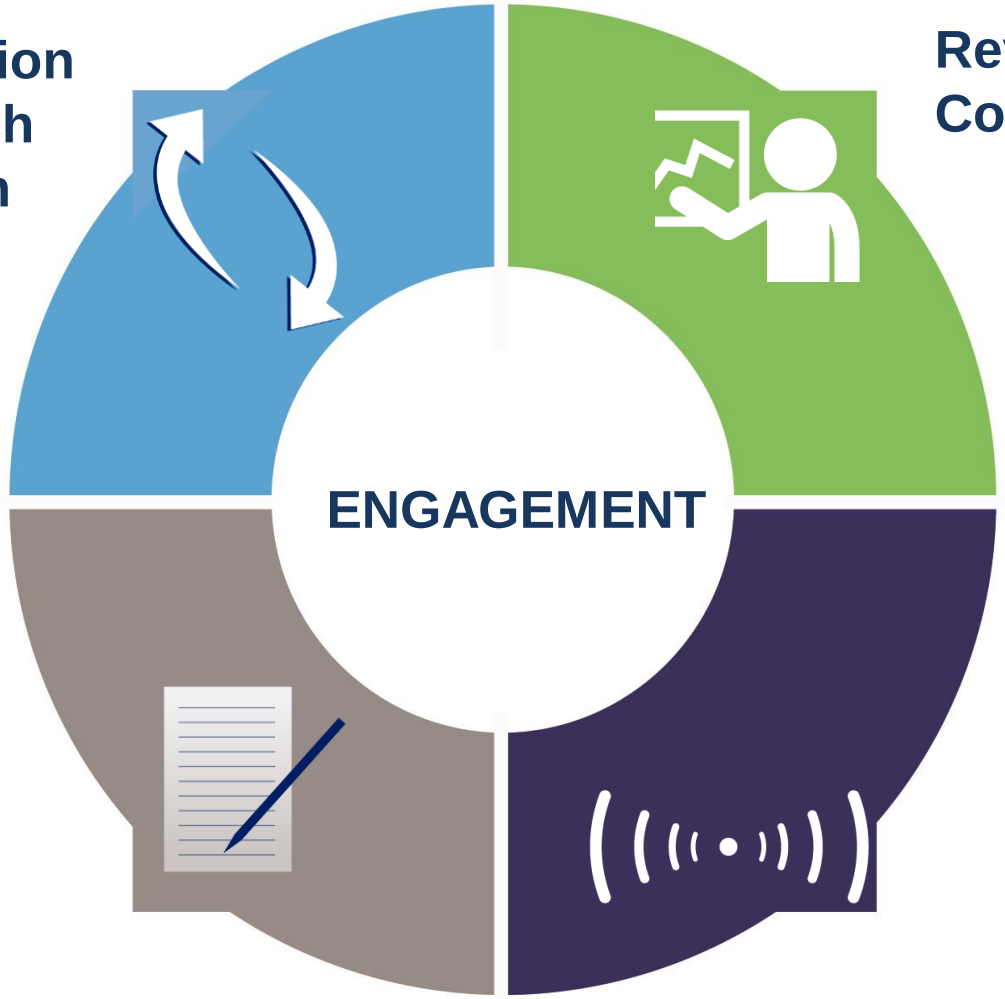
Engagement as a Path To Useful, High-Quality Research



Topic Selection and Research Prioritization

Review, Design, and Conduct of Research

Dissemination and Implementation of Results

Evaluation

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Who are our reviewers?

All reviewers

- Interest in and understanding of PCORI's mission and vision
- Experience with/Interest in PCORI's areas of interest
- Dedication to making a contribution to health care research

Patient and Stakeholder Reviewers

- Ability to represent the perspective of broad or specific patient and stakeholder groups
- Ability to contribute a unique healthcare system perspective

Scientist Reviewers and Chairs

- Advanced degree in health or research-related field
- Publication of relevant peer-reviewed articles/studies
- Current or recent funding in a relevant field of study

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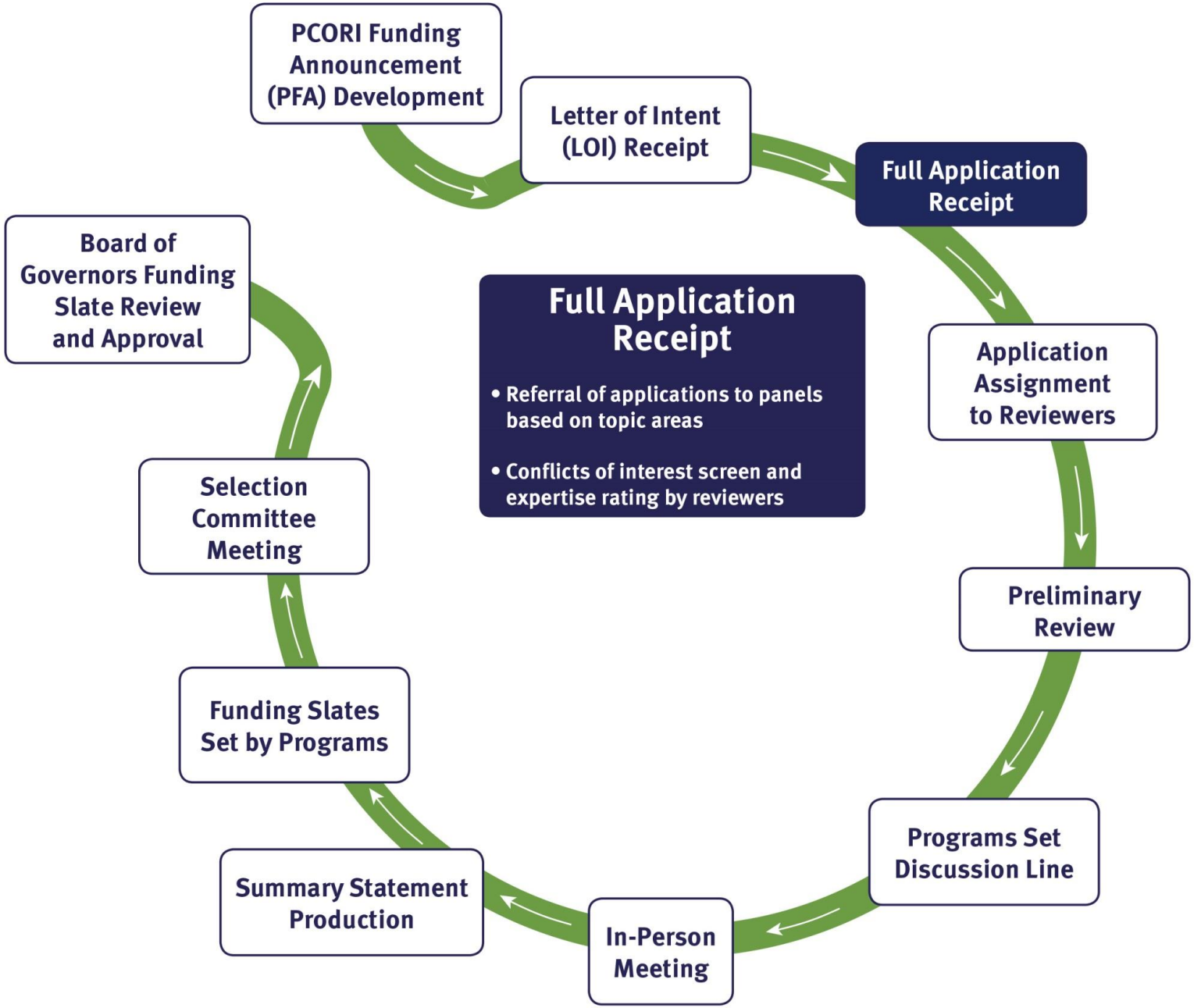
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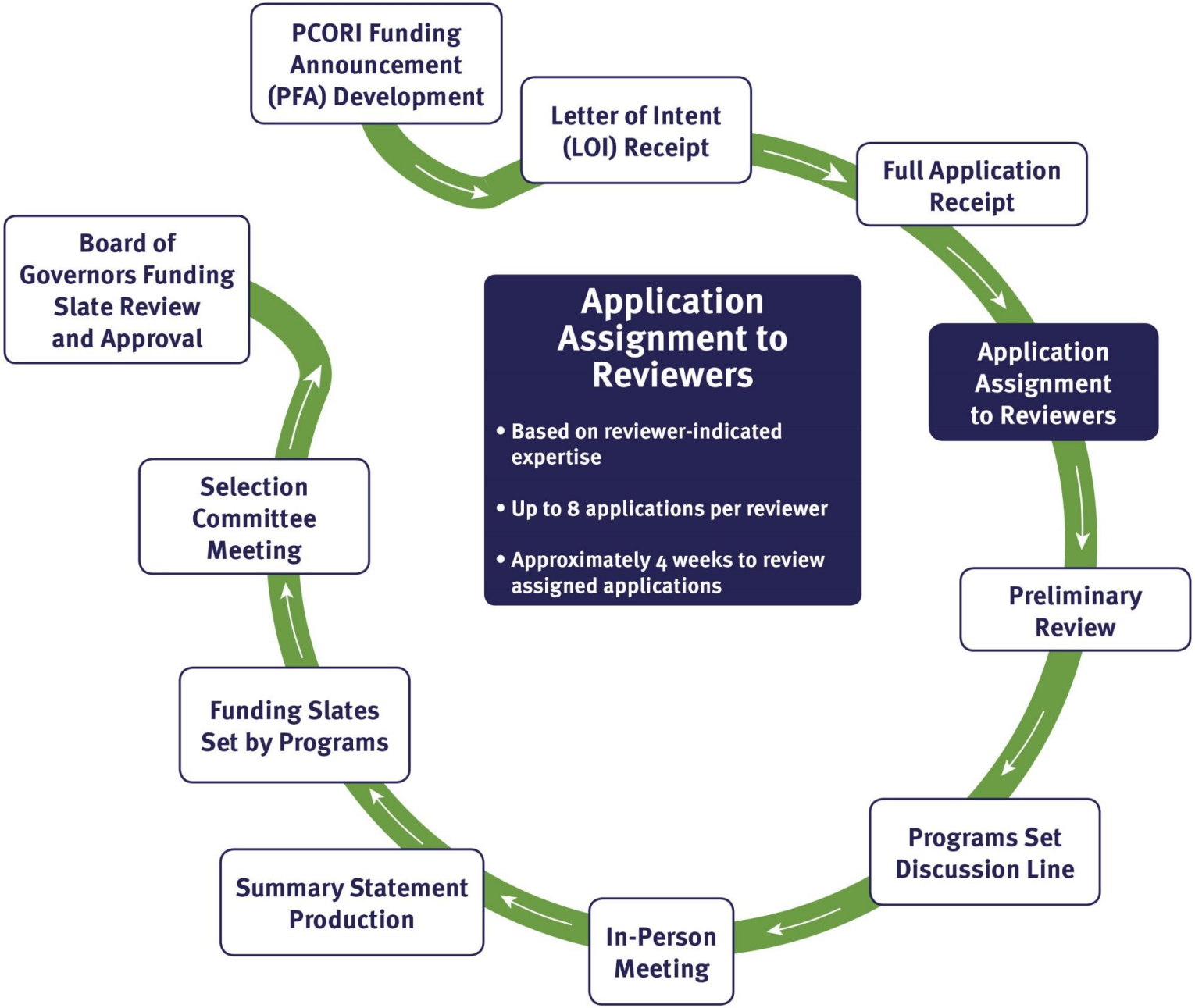
Full Application Receipt
• Referral of applications to panels based on topic areas
• Conflicts of interest screen and expertise rating by reviewers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Application Assignment to Reviewers
• Based on reviewer-indicated expertise
• Up to 8 applications per reviewer
• Approximately 4 weeks to review assigned applications
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Programs Set Discussion Line
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Application Assignments

- Assignments made based on
  - Expertise
  - COI review
- Up to 8 applications per reviewer
- Reviewer training is provided for ALL panel members
  - Mentor program supplements training for patient and stakeholder reviewers
  - Web-based
  - Program-led webinars
- Approximately 4 weeks to review assigned applications

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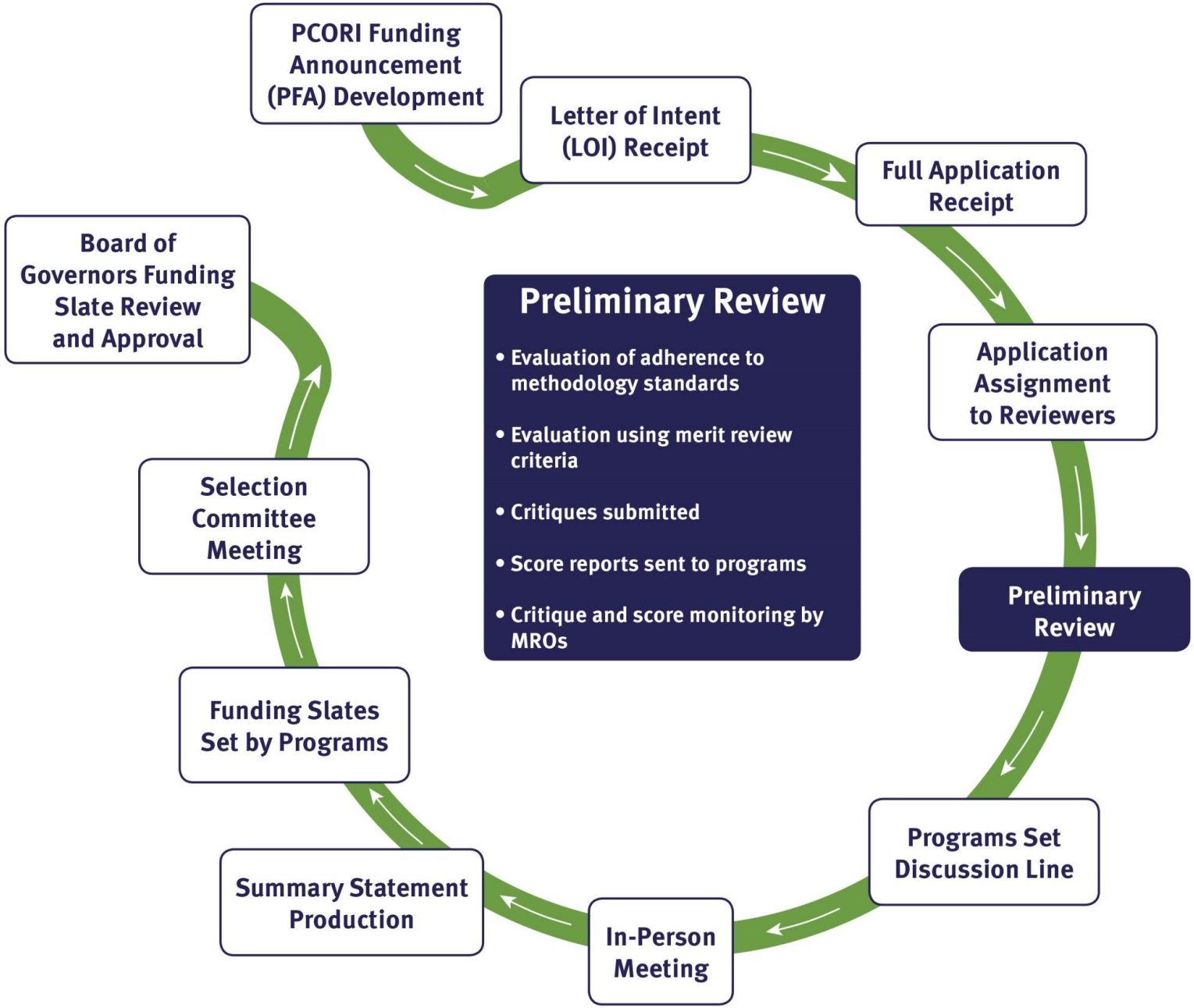
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Preliminary Review
• Evaluation of adherence to methodology standards
• Evaluation using merit review criteria
• Critiques submitted
• Score reports sent to programs
• Critique and score monitoring by MROs

Merit Review Criteria

	Patient and Stakeholder Reviewers	Scientist Reviewers
 **Criterion #1:** Impact of the condition on the health of individuals and population		✓
 **Criterion #2:** Potential for the study to improve healthcare and outcomes	✓	✓
 **Criterion #3:** Technical merit		✓
 **Criterion #4:** Patient-centeredness	✓	✓
 **Criterion #5:** Patient and stakeholder engagement	✓	✓

Impact of the condition on the health of individuals and populations

The proposal addresses the following questions:

- Is the condition or disease associated with a significant burden in the US population, in terms of prevalence, mortality, morbidity, individual suffering, or loss of productivity?
- **Alternatively, does the condition or disease impose a significant burden on a smaller number of people who have a rare disease?**
- Does the proposal include a particular emphasis on patients with one or more chronic condition?

We Advance Research Methodology

We have adopted methodology standards that all research should follow, at a minimum

Methodology Standards: 11 Broad Categories

- Formulating Research Questions
- Patient-Centeredness
- Data Integrity and Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects
- Data Networks
- Data Registries
- Adaptive and Bayesian Trial Designs
- Causal Inference
- Studies of Diagnostic Tests
- Systematic Reviews

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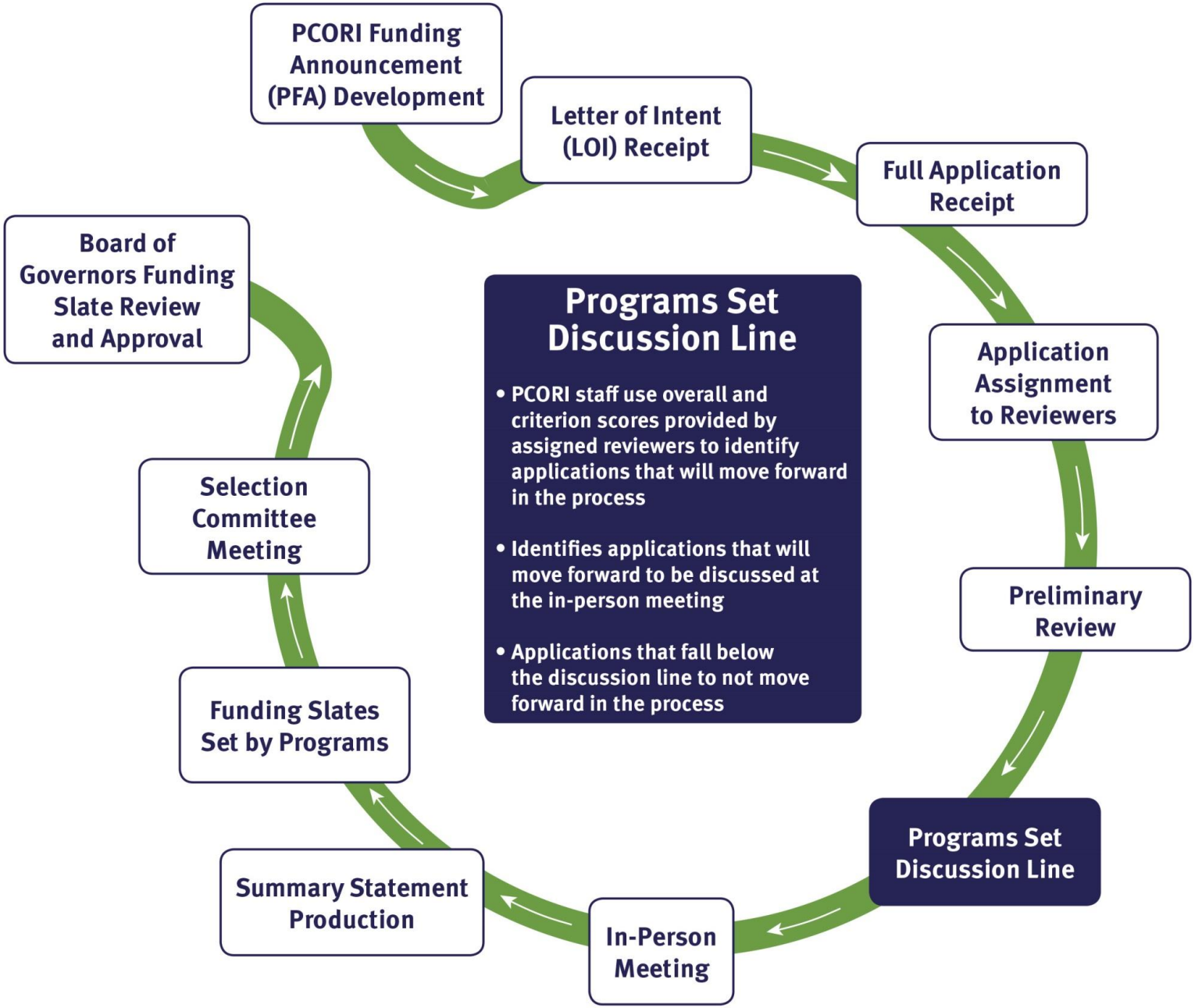
Scoring Range

The scoring range consists of a nine point scale.

A score of 1 indicates an exceptionally strong application.

Range	Score	Descriptor	Characteristics
High	1	Exceptional	Exceptionally strong with essentially no weaknesses
	2	Outstanding	Extremely strong with negligible weaknesses
	3	Excellent	Very strong with only some minor weaknesses
Medium	4	Very Good	Strong but with numerous minor weaknesses
	5	Good	Strong but with at least one moderate weakness
	6	Satisfactory	Some strengths but also some moderate weakness
Low	7	Fair	Some strengths but with at least one major weakness
	8	Marginal	A few strengths and a few major weaknesses
	9	Poor	Very few strengths and numerous major weaknesses

A score of 9 indicates an application with serious and substantive weaknesses.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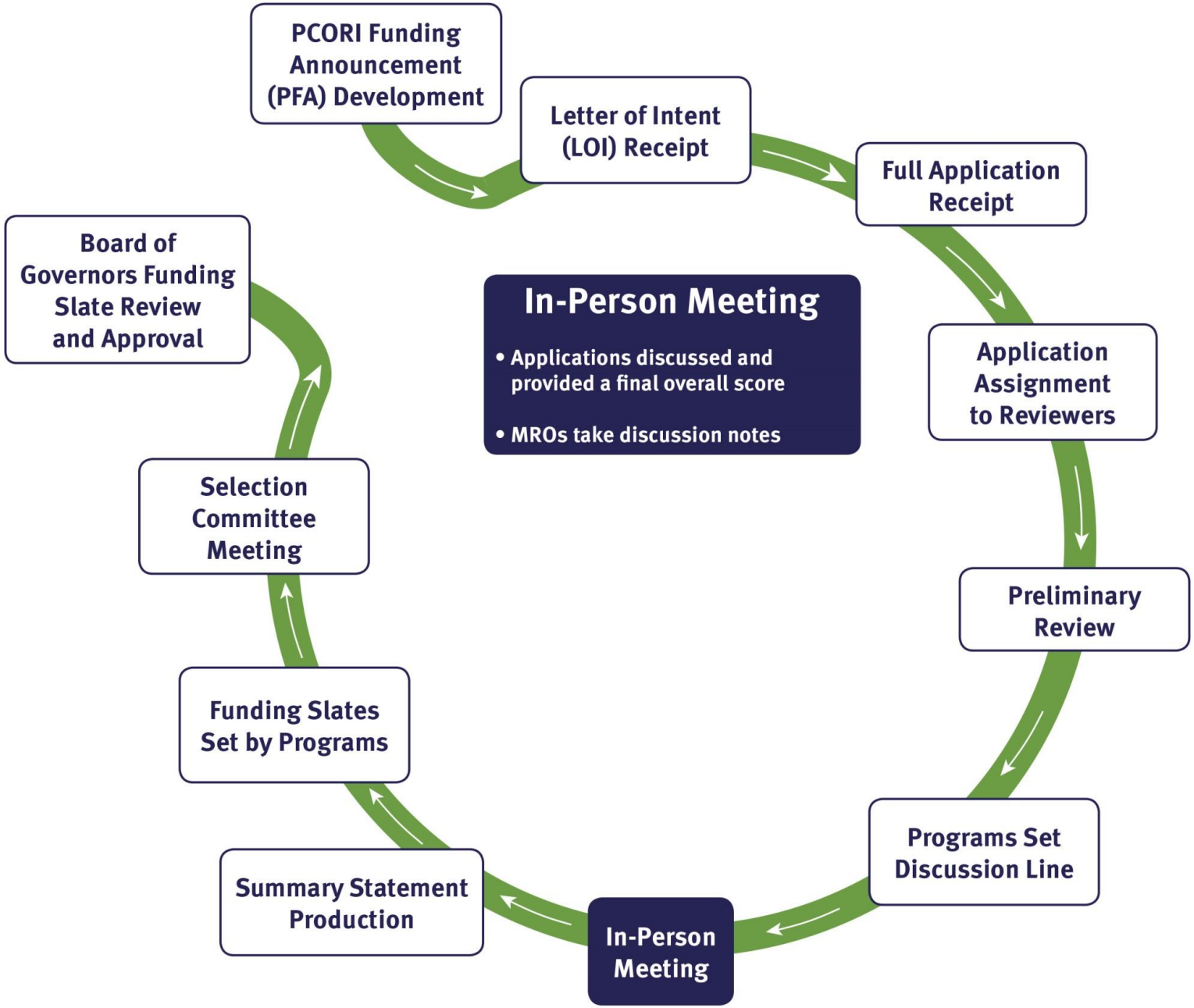
Programs Set Discussion Line
• PCORI staff use overall and criterion scores provided by assigned reviewers to identify applications that will move forward in the process
• Identifies applications that will move forward to be discussed at the in-person meeting
• Applications that fall below the discussion line to not move forward in the process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In-Person Meeting
• Applications discussed and provided a final overall score
• MROs take discussion notes

Merit Review In-Person Meeting

Reviewer 1: Scientist 1 → **Reviewer 2: Patient** → **Reviewer 3: Stakeholder** → **Reviewer 4: Scientist 2**

Description
Chair briefly introduces application
Scientific Reviewer #1: summarizes application strengths/weaknesses and score
Patient reviewer: summarizes application strengths/weaknesses and score
Stakeholder Reviewer: summarizes application strengths/weaknesses and score
Scientific Reviewer #2: summarizes application strengths/weaknesses and score
General panel discussion
Chair summarizes panel discussion of application
Full panel scores application in PCORI Online

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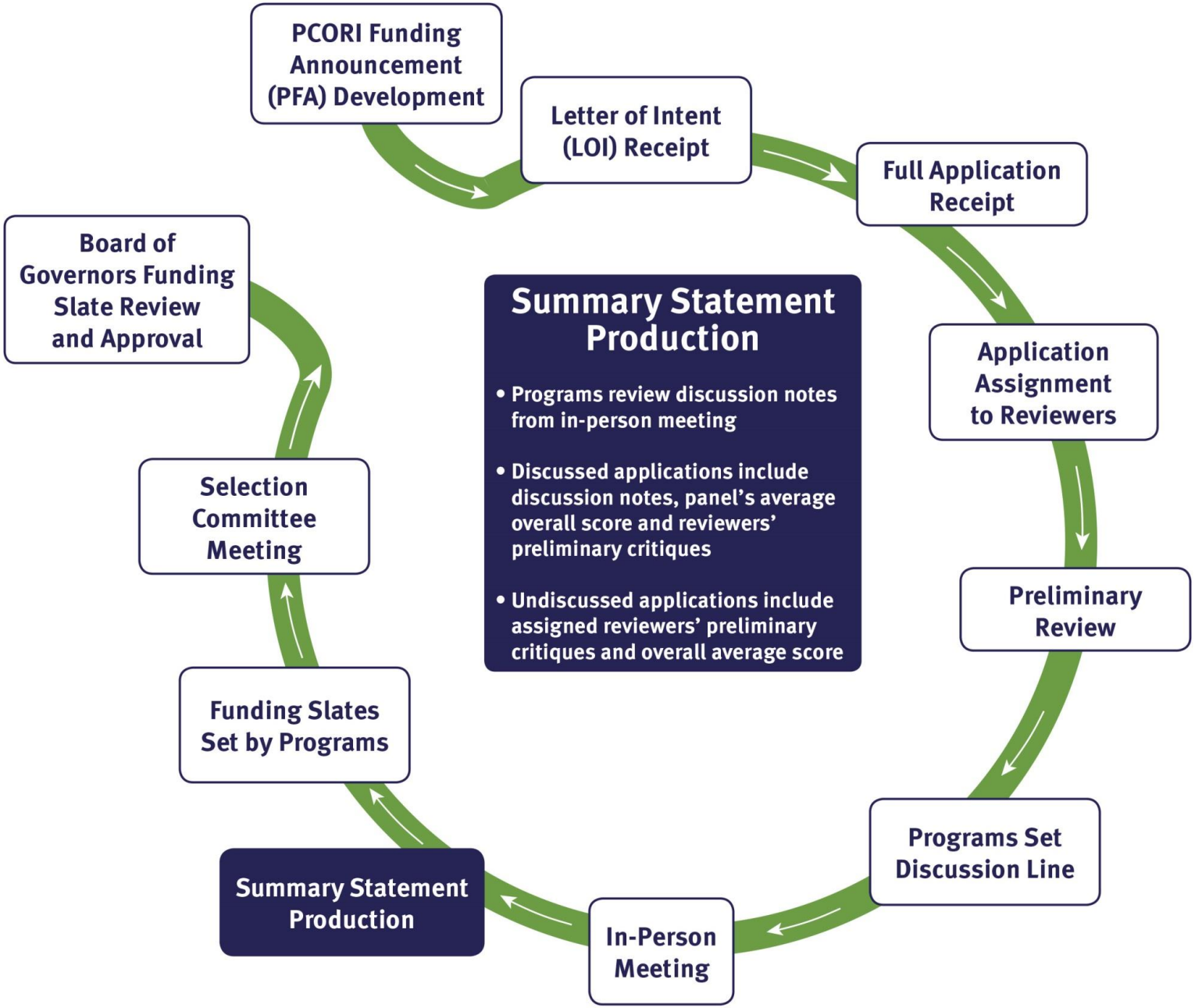
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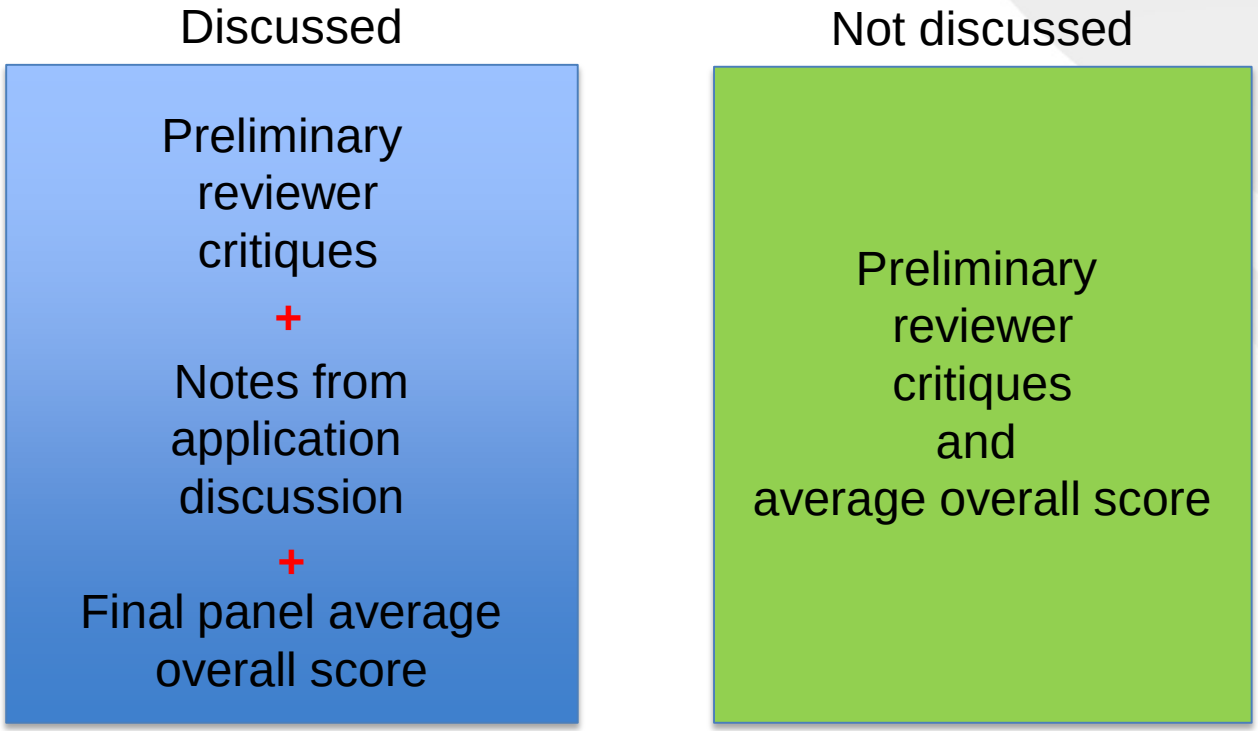
Full Application Receipt
Application Assignment to Reviewers
Preliminary Review
Programs Set Discussion Line
In-Person Meeting
Summary Statement Production
Funding Slates Set by Programs
Selection Committee Meeting
Board of Governors Funding Slate Review and Approval
Summary Statement Production
• Programs review discussion notes from in-person meeting
• Discussed applications include discussion notes, panel's average overall score and reviewers' preliminary critiques
• Undiscussed applications include assigned reviewers' preliminary critiques and overall average score

Summary Statements

- All applicants receive a summary statement at the end of the review cycle



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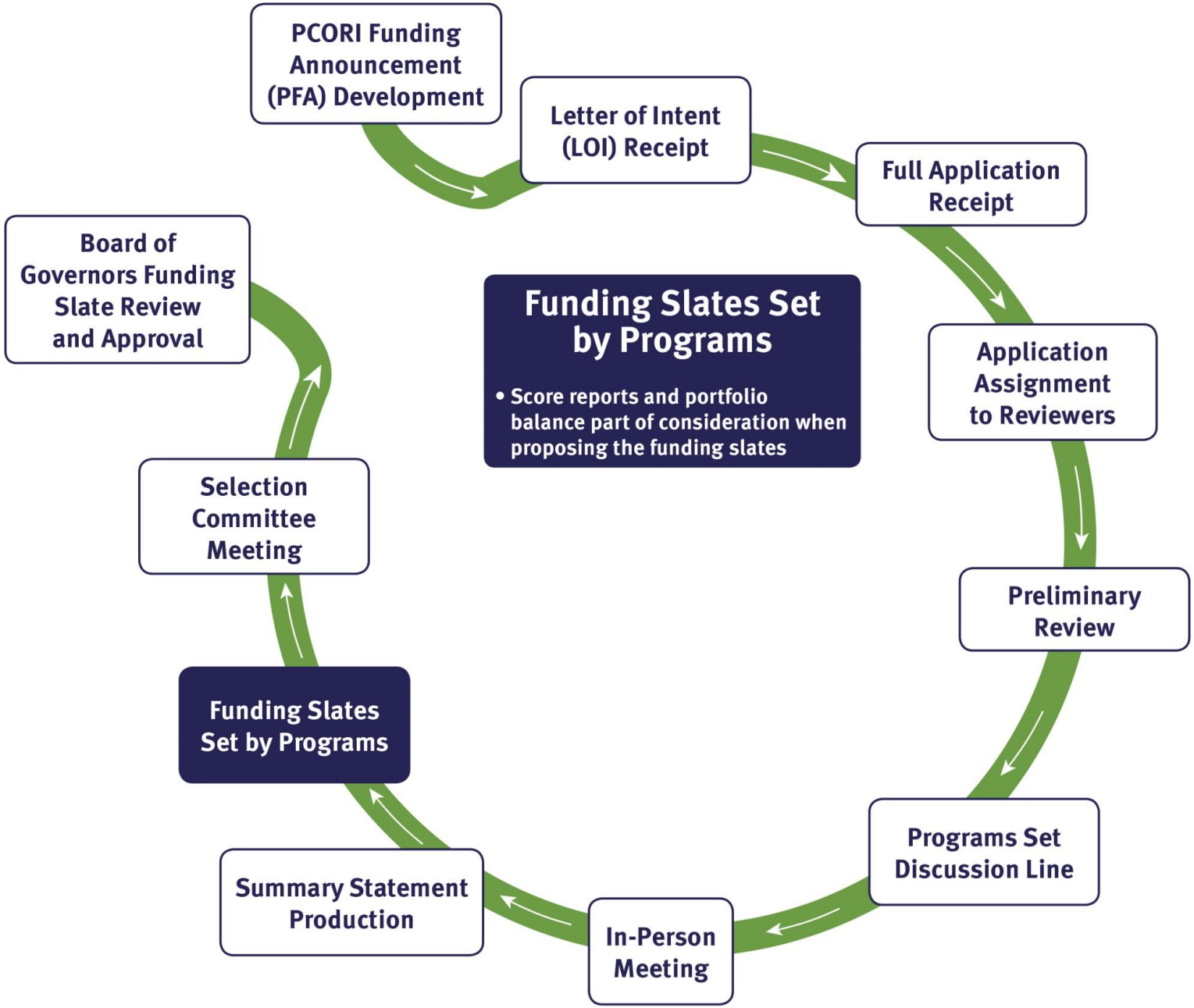
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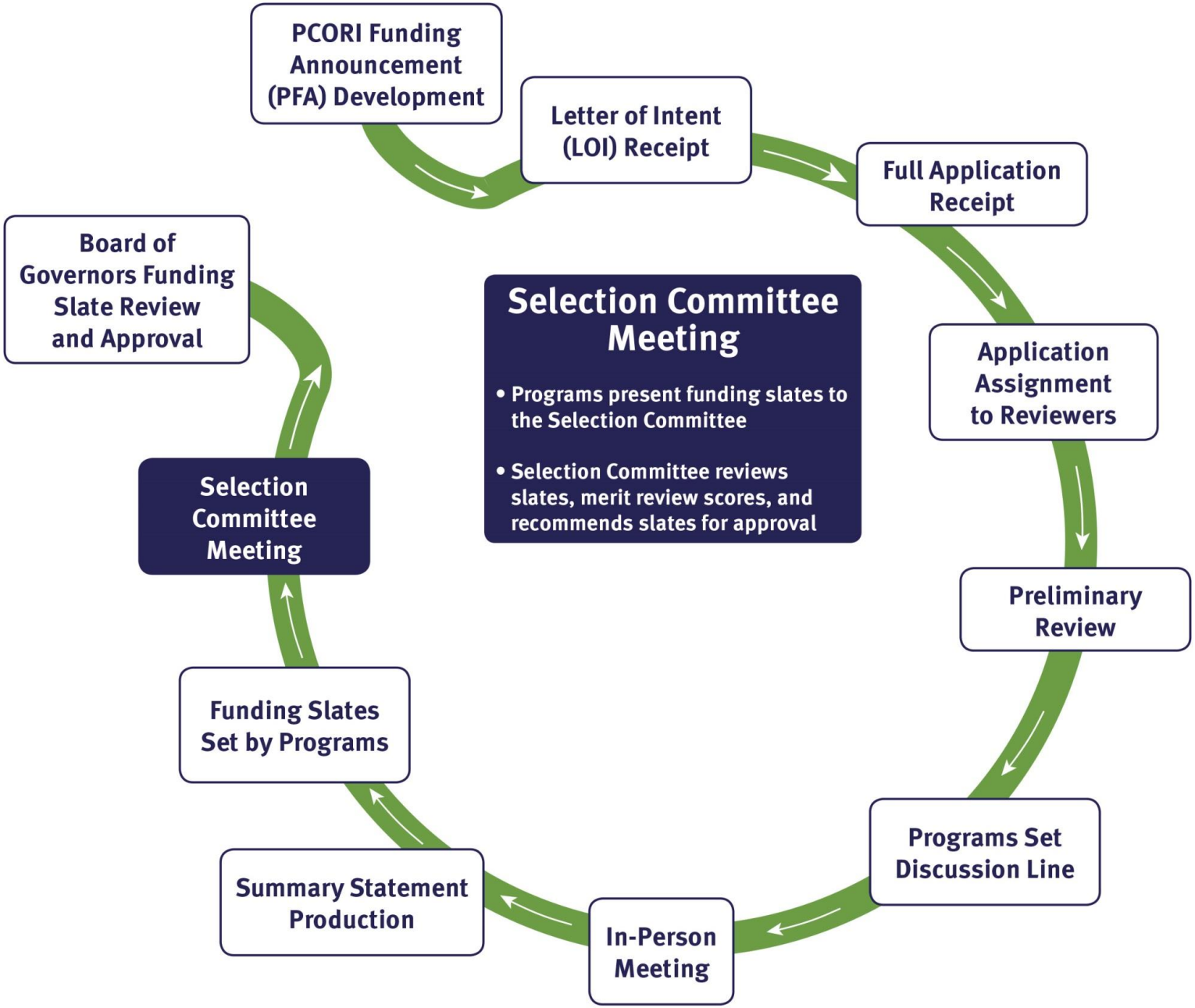
Funding Slates Set by Programs
• Score reports and portfolio balance part of consideration when proposing the funding slates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Selection Committee Meeting
• Programs present funding slates to the Selection Committee
• Selection Committee reviews slates, merit review scores, and recommends slates for approval

Funding Slates and Selection Committee

- Portfolio information presented to Selection Committee, along with
  - Proposed slate
  - Rationale for application selection
- Facilitates selection of applications that best support our mission for recommendation to the Board

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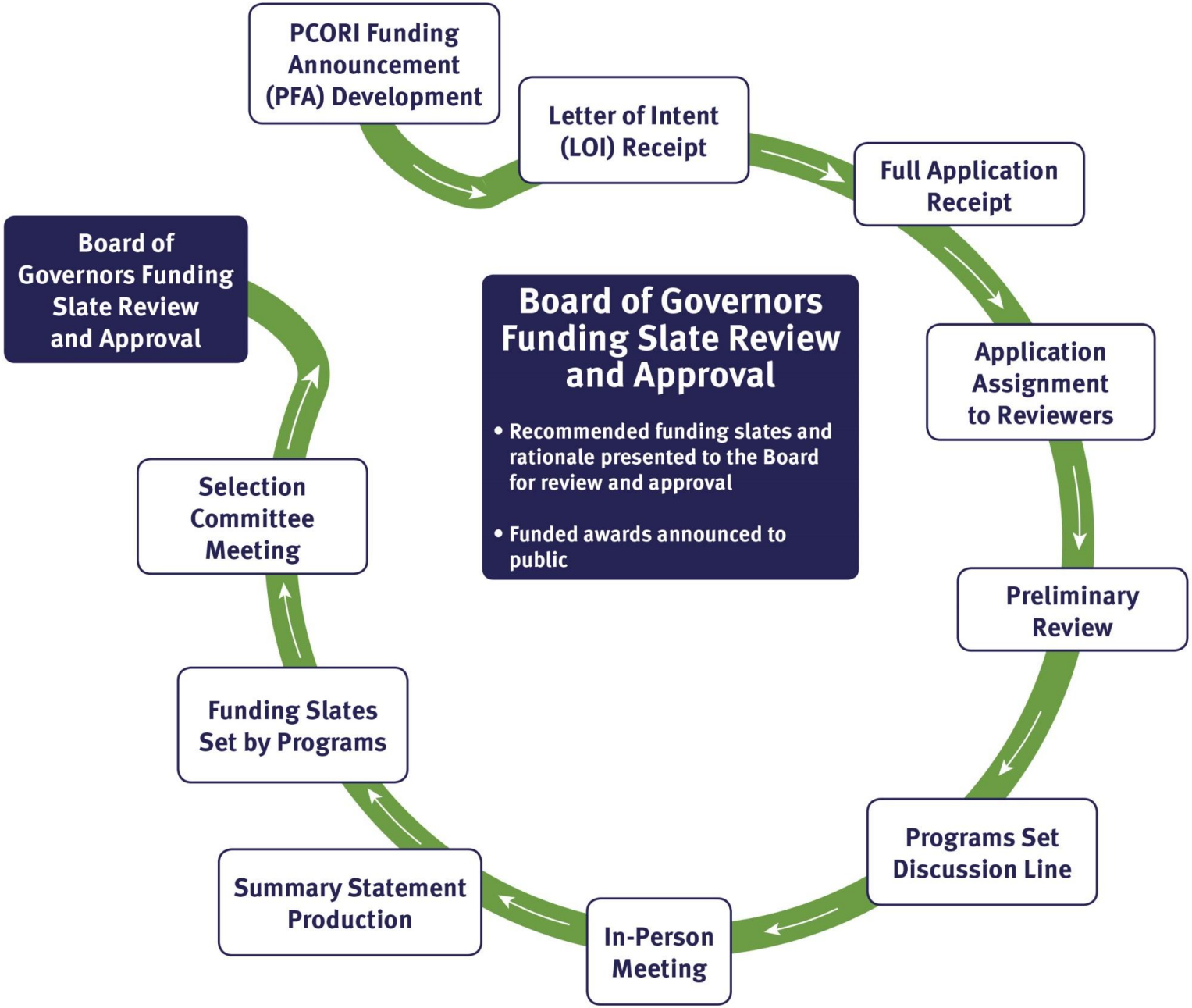
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Board of Governors Funding Slate Review and Approval
• Recommended funding slates and rationale presented to the Board for review and approval
• Funded awards announced to public

Rare Disease Submitted Topics

Greg Martin
Deputy Director of Stakeholder Engagement, PCORI

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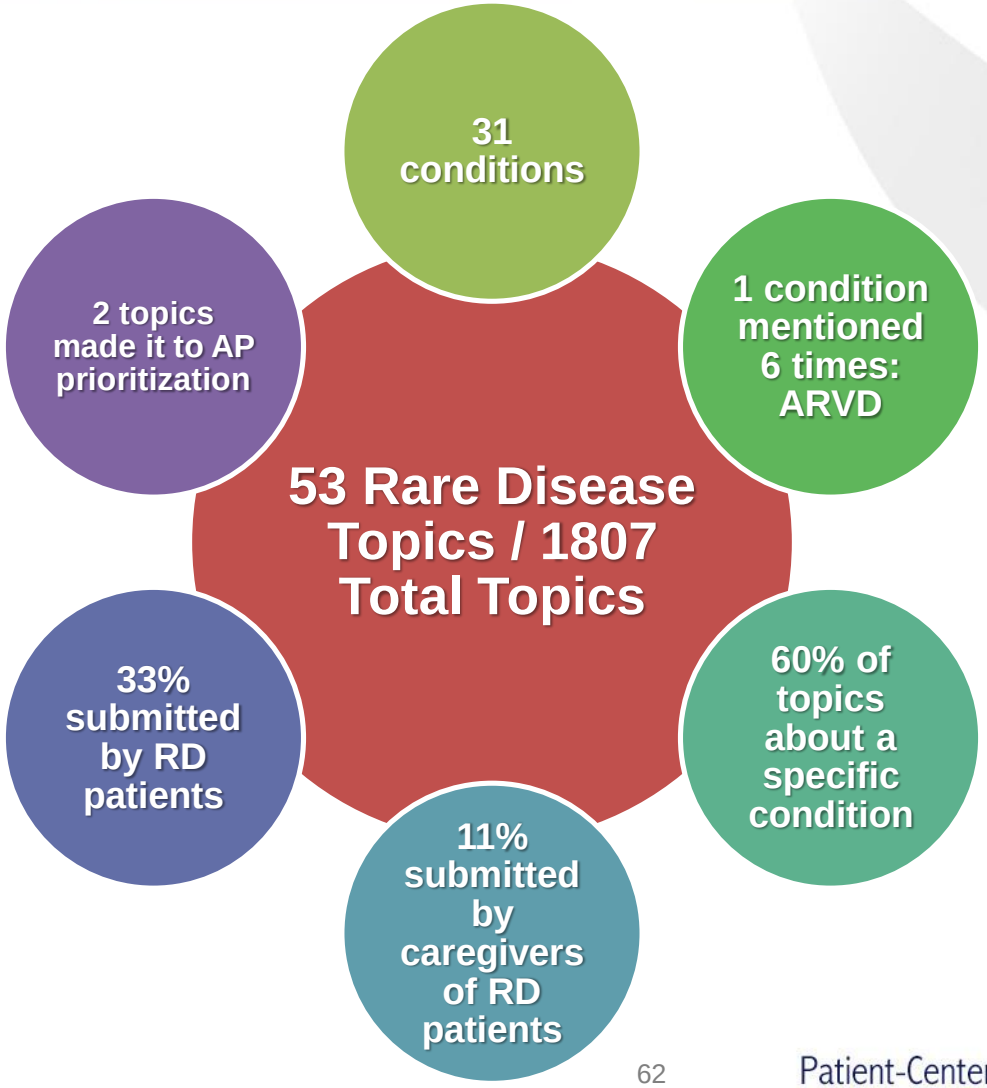
Summary of Submitted RD Topics



Cross-Cutting VS Condition-Specific Topics

- Example of a cross-cutting CER RD topic:
  - Is molecular genetic testing more effective than traditional clinical methods for diagnosis of rare diseases?
- Example of a rare disease specific topic:
  - Is early bone marrow transplant treatment for children affected by adrenoleukodystrophy (ALD) more effective than late bone marrow transplant treatment?

Cross-Cutting Rare Disease Issues

Naomi Aronson, Ph.D
Methodology Committee, PCORI

Patient-Centered Outcomes Research Institute

Methodologic Issues

- Methodologic issues and standards in research in rare diseases
- Strength of evidence framework for systematic review
- Standard definition/taxonomy

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Cross Cutting Research Issues: Quality of Life

- What is the CER question?

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Disease or Treatment Symptoms

- Fatigue
- GI symptoms
- Neuropathies
- Depression/anxiety
- Adverse events
- Sexual activity

Navigating Care

- Coordinating complex care
- Diagnosis and referral
- Self-management
- Pediatric vs. adult
- Cost of care

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Social Environment

- Employment
- Family Relationships
- Social Relationships

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CER Topics

David Hickam, MD

Program Director, Clinical Effectiveness Research, PCORI

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What is CER?

- Comparative Effectiveness Research
  - Focus on the choices people make about the options for managing a disease.
  - Compare the benefits and harms associated with each option.

What is PCORI interested in?

- Questions that:
  - Compare the effectiveness of 2 or more strategies for prevention, treatment, screening, diagnosis, or management of a condition; compare alternative system-level approaches
  - Compare factors that may affect patients' adherence to treatments.
  - Help to address disparities in health care
  - Improve the communication of research findings
  - Advance methods for patient-centered outcomes research

Key Features of Research Supported by PCORI

Research Should:

- Study the benefits and harms of interventions and strategies delivered in *real-world settings*
- Compare at least two alternative approaches
- Be based on health outcomes that are meaningful to the patient population
- Be likely to improve current clinical practices

Key Features of Research Supported by PCORI

Special Topics of Interest:

- Conditions that heavily burden patients, families and/or the health care system.
- Chronic or multiple chronic conditions
- Rare and understudied conditions
- Conditions for which outcomes vary across subpopulations

How to Formulate a CER Question

What you will need:

- Patient population of focus
  - Parents of children with leukemia
  - Smokers with depression
- Health care decision(s)
  - Choosing a treatment of a new episode of low back pain
  - Choosing a care management program for mental illnesses
- Clinical interventions to be compared
  - Clinical intervention VS an alternative treatment or intervention
  - Clinical intervention VS usual care (if the components of this care are well defined)

What you will need to exclude:

Cost-effectiveness analysis (CEA)

Examples

- Which of the three common medication used to treat pediatric LRE (levetiracetam, lamotrigine, or oxcarbazepine) will maximize cognitive abilities in children with LRE, and minimize cognitive side effect risks?
- How do clinic enhancement and system integration, home visits with CHWs, and health plan enhancement compare for improving asthma outcomes among low income African Americans and Latino patients in Seattle?
- What are comparative benefits and risks of nursing home, assisted living and home-based care for elderly patients with dementia?

Information to Increase the Meaningfulness of the CER Question

- Meaningful difference in study endpoints from the patient population's perspective
- Gap(s) in evidence
- Significant burden in the US population
- Likelihood of implementation in practice

Outreach and Other Solutions – Open Discussion

Greg Martin

Deputy Director of Stakeholder Engagement, PCORI

Patient-Centered Outcomes Research Institute

Recap and Next Steps

Marshall L. Summar, MD
Chair, Advisory Panel on Rare Disease, PCORI
Vincent Del Gaizo, Co-Chair
Advisory Panel on Rare Disease, PCORI
Bryan Luce, PhD, MBA
Chief Science Officer, PCORI

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Adjourn