A Framework for Defining Evidentiary Criteria for Biomarker Qualification

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Goals of the Workshop

- To enhance clarity, predictability, and harmonization of the biomarker qualification process with a standard framework

- Improve the quality of BQ submissions to FDA

- Support FDA in the development of relevant Guidance(s) for Evidentiary Criteria in biomarker qualification

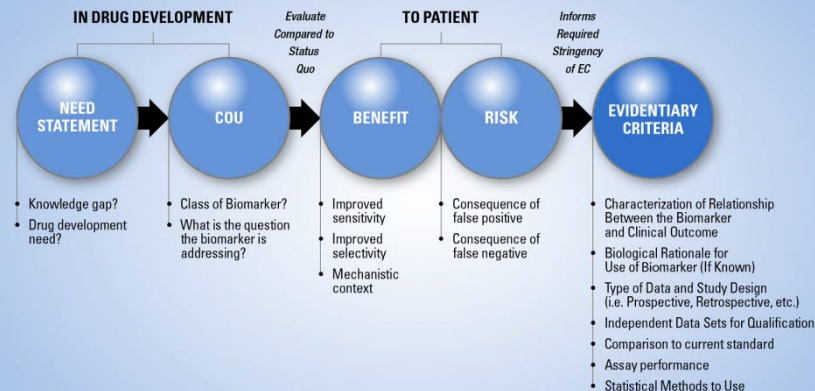# Biomarker qualification: Clarity, predictability, harmonization

The Proposed Five-Component Process

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
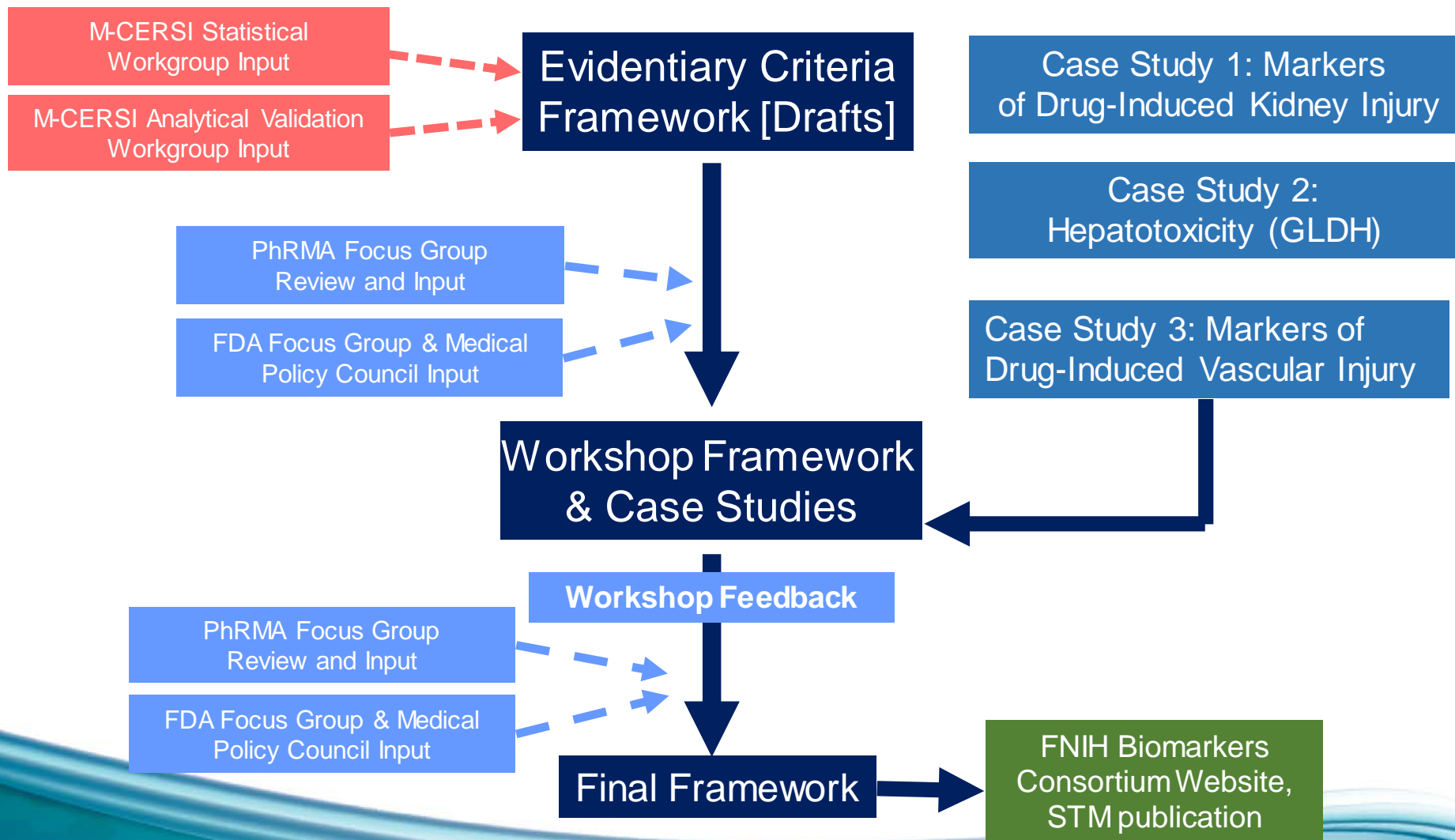
January 2014
Procedural

Biomarker Qualification Workshop
Framework for Defining Evidentiary Criteria

Wireless Internet Passcode:
BIOMARKERS

General Evidentiary Criteria Document Development

What does the framework provide?

- A clear set of steps needed for working toward Biomarker Qualification

- Identify key areas for defining biomarker need

- Specify and limit biomarker development focus to allow successful generation of appropriate evidence

- Provide consistent set of characteristics to describe and define the biomarker development program with the regulatory agency
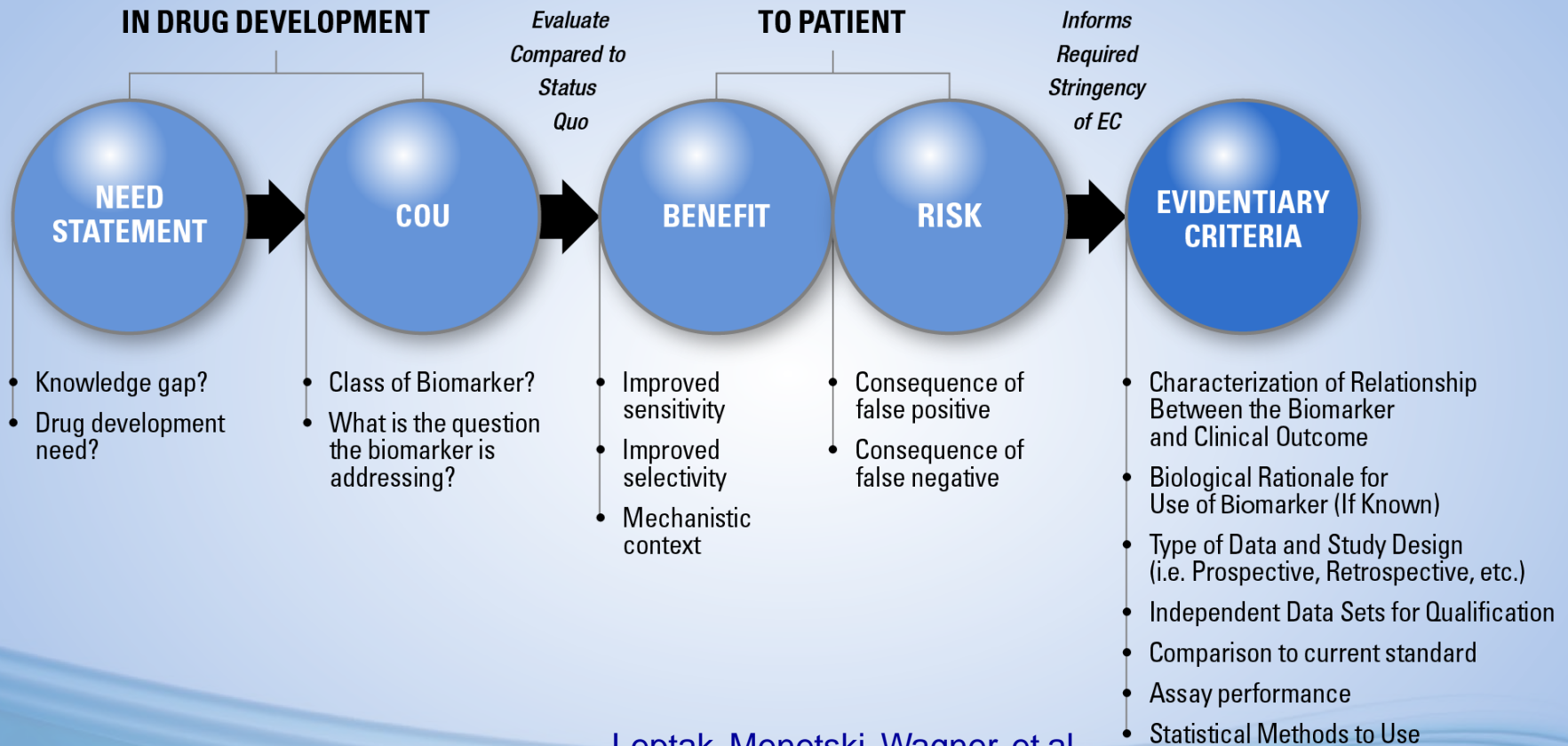
Primary Assumption:

A clearly defined goal to the project will provide a better view of a path to ultimate drug development decision making and regulatory approval.

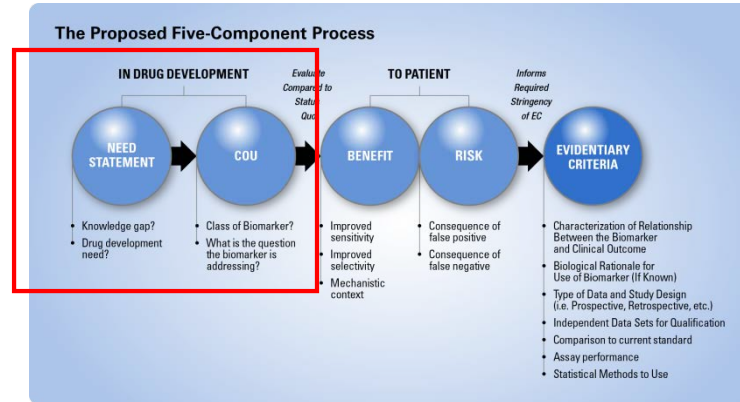*The framework provides a context for the discussion between sponsor and the agency.*

Constructing a biomarker road map

The Proposed Five-Component Process

Leptak, Menetski, Wagner, et al.
Sci Transl Med. 9(417), 2017

Need statement and context of use (COU)

The Proposed Five-Component Process

- Need statement
  - The nature and extent of the need, drug development issue it addresses and target population
  - The major challenge(s) and unique aspects of these challenges the project is to address
  - The reasons and causes for the deficit being addressed
- COU statement – concise description of how a biomarker is intended to be used in drug development
- COU simplified to only 2 elements:
  - What class of biomarker is proposed and what information content would it provide?
  - What question is the biomarker intended to address? ("What is the biomarker's specific fit-for-purpose use?")

Examples of COU

The Proposed Five-Component Process

BEST: identify likelihood of a clinical event

A prognostic marker for disease progression to be used as an inclusion criteria in a Phase 2 clinical trial of a novel drug to enrich for the likelihood of organ transplantation.

Clinical Trial Decision

BEST: response to an intervention or exposure.

A safety marker for organ toxicity to be used in a Phase 1 clinical trial of a novel drug in addition to a standard measure of organ toxicity to explore and refine the clinical trials stopping criteria.

Clinical Decision

Benefit and risk

The Proposed Five-Component Process
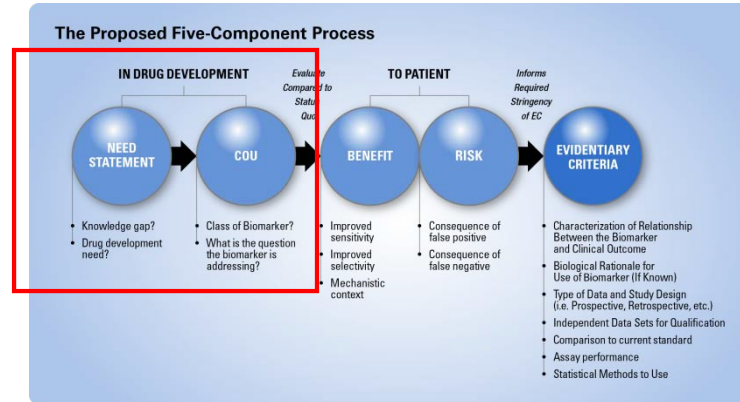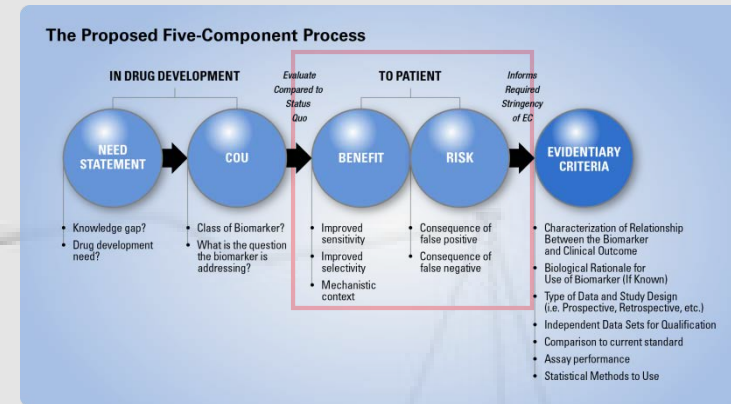
- The benefit and risk profile, given that the COU is related to the biomarker's value to drug development or clinical trials, is assessed from the perspective of patients

- Benefit assessment
  - What are the unmet needs of the population defined in the COU?
  - What is the mortality and morbidity of the disease's natural history in the absence of treatment?
  - What is the severity of the disease or condition?
  - What is the perceived benefit of the new biomarker vs. the current standard?

- Risk assessment
  - What is the potential consequence or harm if the biomarker's performance is not aligned with expectations based on the COU?
  - What is the perceived incremental risk, new biomarker vs. current standard?
  - When in the drug development lifecycle is the biomarker intended use?
  - What is the scope of the biomarker COU in terms of impacting drug development and regulatory review?

Examples of benefit and risk analyses

The Proposed Five-Component Process
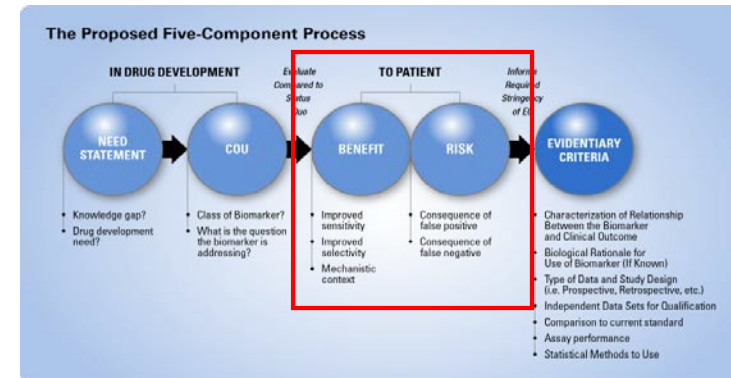
- Favorable benefit and risk profile – lower level of evidence
  - Stratification of patients to ensure equal distribution of biomarker positive and biomarker negative individuals in the different arms of a clinical trial
  - If biomarker does not perform – loss of resources but not patient safety

- Less favorable benefit and risk profile – moderate level of evidence
  - Safety biomarker used in addition to the traditional safety biomarkers
  - Degree of risk depends on the impact on decision-making in drug development and the risk to patients enrolled in the trials

- Challenging benefit and risk profile – higher level of evidence
  - Surrogate endpoint
  - If the biomarker is not truly a surrogate endpoint for predicting clinical benefit, results invalid and inappropriate approval decisions made
  - Leads to potentially ineffective drugs marketed or patients denied access to effective therapy

Evidence map

The Proposed Five-Component Process
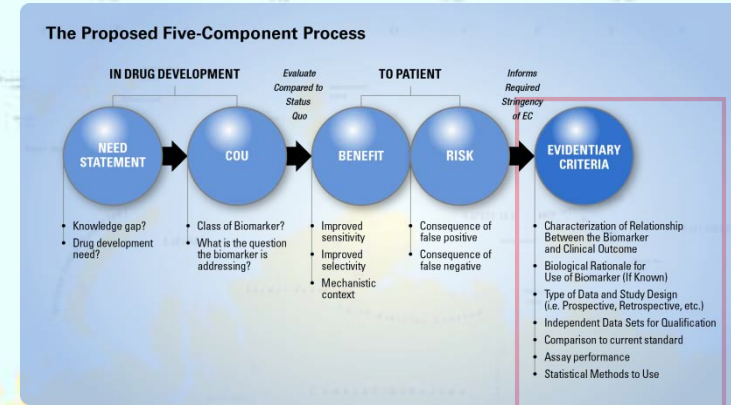
- The evidence maps in this framework are inspired by, but not identical to, the one used by Altar et al. (2008)

- The COU choices made determine the overall relative level of benefit and risk

- Benefit and risk determined as a result of the COU in turn determines the levels of evidence needed to evaluate the biomarker for qualification

- The evidence acceptable for satisfying evidentiary criteria in some cases may be partially or entirely composed of retrospective, literature, or other "real world" types of evidence

- The levels of evidence required to qualify the marker can be described according to a series of variables

Altar et al. CPT, 83:368-371, 2008

Evidence map

The Proposed Five-Component Process

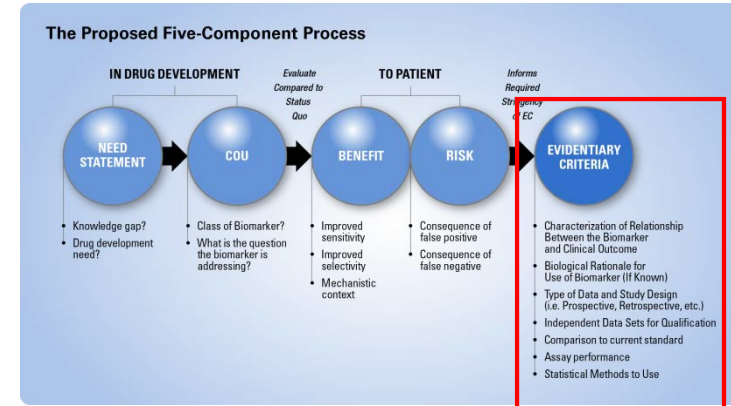| Criterion	High	⟷	Minimal
(1) Assay[1]	Regulatory clearance or approval for marketing as a diagnostic	⟷	"Fit-for-purpose" validation with acceptable performance characteristics
(2a) Scientific Understanding[2]	Causal biological links established between the disease, the intervention and the biomarker	⟷	Gaps in causal links and/or analyte identity
(2b) Scientific Understanding: Data source for comparison of disease to marker	Well designed with focused analysis on one or a small number of biomarkers	⟷	Biomarker discovery analysis from an exploratory trial or dataset
(3) Biological Performance Expectations[3]	Low potential for false result	⟷	Improved performance over current state: [e.g., current standard if available]
(4) Types of data and samples proposed to establish qualification	Prospective double-blind control study or confirmed results in multiple independent data sets	⟷	Retrospective analysis of published results
(4a) Quality of clinical data source: Prospective study	Focused, randomized appropriately powered trial	⟷	Narrow subgroup of intended population, small, or exploratory trial with multiple measures and lack of correction for multiple comparisons
(4b) Quality of clinical data source: Retrospective study	Large population, well controlled combined/meta analysis or multiple studies independently confirming results	⟷	Small, or exploratory trial with multiple measure that is not appropriately powered for significance
(5a)[4] Statistical evidence of the relationship of the biomarker to clinical outcomes	Conclusive across multiple studies	⟷	Some evidence in the literature
(5b) Statistical evidence on the usefulness of the biomarker threshold for significance	Significantly better than current standard (could be in combination with the current standard)	⟷	Similar or slightly better than current standard

Analytical validation

The Proposed Five-Component Process

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity
- Reportable range
- Reference interval
- Reproducibility
- Stability

| Very High Standard:	Minimum Requirements:
Regulatory Marketing Approval as Diagnostic	"Fit-for-Purpose" Validation
Parameters Evaluated During Validation	
Accuracy Precision Analytical sensitivity Analytical specificity Reportable range Reference interval Reproducibility Stability Other as required	Accuracy Precision Analytical sensitivity Analytical specificity Reportable range Reference interval Other as required

The process is dynamic and interactive

Workflow and Decision Process Summary
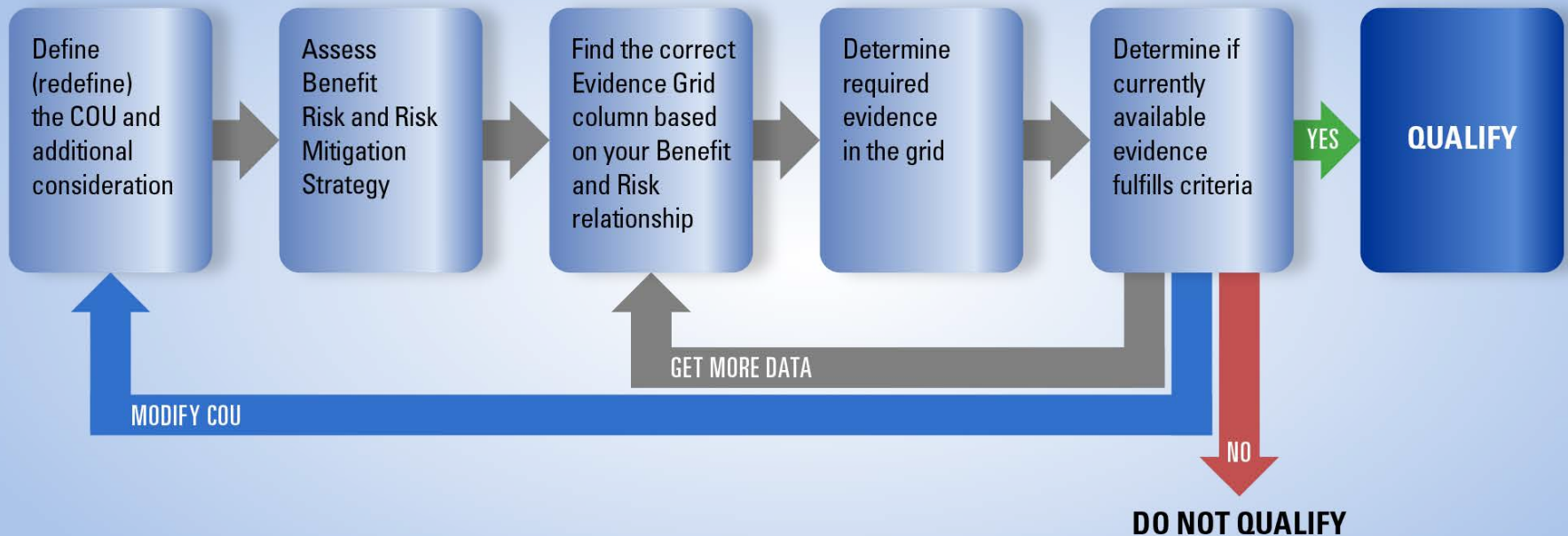
Conclusion

- Alignment from multiple, diverse stakeholders

- Consistent, comprehensive, semi-quantitative parameters for biomarker qualification

- Greater degree of clarity, predictability, and harmonization

- Broadly applicable across multiple categories of biomarkers and COUs

- Since each category of biomarker and COU has unique factors to consider as part of the development process, multiple modules are proposed to address these more specific issues

Key Outcomes and Action Items from the Workshop

Main Findings

- Overall agreement on the validity of the framework and its utility to advance qualification of drug safety biomarkers

Action items

✓ Revise documents to support FDA Guidances (FNIH Biomarkers Consortium Website, STM publication)
- "Mother" Guidance on evidentiary criteria for biomarker qualification (framework): conceptual, succinct, understandable
- Baby Guidance #1 on applicability of framework to safety biomarkers, with specific examples of evidence based on case studies
- Additional Baby Guidances (#2 and #3) on Analytical Validation and Statistics (may require additional workshops)

✓ Workshop on Analytical Validation (Duke-Margolis)
- Generate a guidance that covers diagnostics and biomarker qualification

✓ Develop and pilot a 'safe harbor' database to serve as a repository for progressive qualification of biomarkers (C-Path Biomarker Data Repository)

✓ ***Apply similar approach used in this workshop to clarify the evidentiary standards needed to qualify surrogate (efficacy) endpoints (today)***

Thanks to .com, .edu, .gov, and.org!

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- **AND all those who attended the Workshop!**