Evidentiary Considerations for Integration of Biomarkers In Drug Development: Safety Biomarkers

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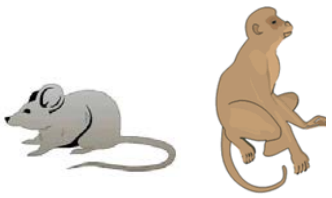
10 YEARS

Translational Safety Biomarkers

Monitorability of Drug Induced Tissue Injury

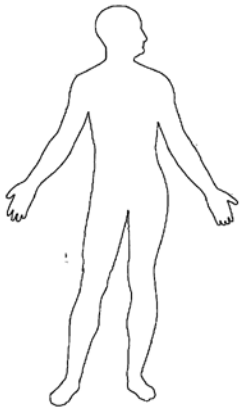
Adverse outcomes in animals



Histopathology

Better Monitoring of Potential Safety Liabilities in Humans

Adverse outcomes in humans



Fluid Based Safety Biomarker

Fluid Based Safety Biomarkers - similar to routine clinical pathology measures that can be used to **accurately predict** drug induced tissue injury in humans

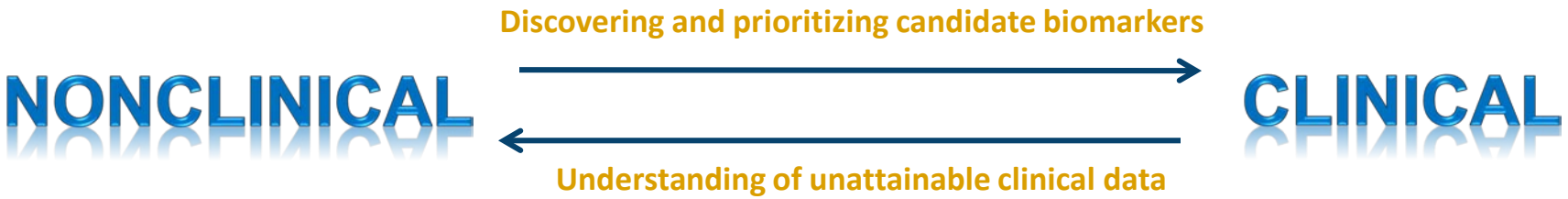
Translational Safety Biomarkers

Nonclinical Studies:

Anchor the novel biomarker's performance to histopathological changes (gold standard biomarker in nonclinical toxicology studies), as well as to standard biomarker performance.

Clinical Studies:

Demonstrate that the novel biomarker outperforms the standard biomarker (gold standard for safety in clinical studies).



Translational Safety Biomarkers

The objective of translational safety biomarker qualification is to demonstrate the **predictive accuracy** of the biomarker to detect tissue injury in humans.

This can be accomplished directly in animals by measuring biomarker concentrations and assessing histopathological changes in target organs (The ***true true*** can be defined and measured).

In clinical studies, demonstration of the predictive accuracy of the biomarker to tissue injury cannot be directly determined as histopathology is rarely evaluated in clinical studies.

Scientific and Regulatory Expectations for Biomarker Qualification

Data Quality Expectations

Well designed, conducted, and documented studies that support the use of the biomarker

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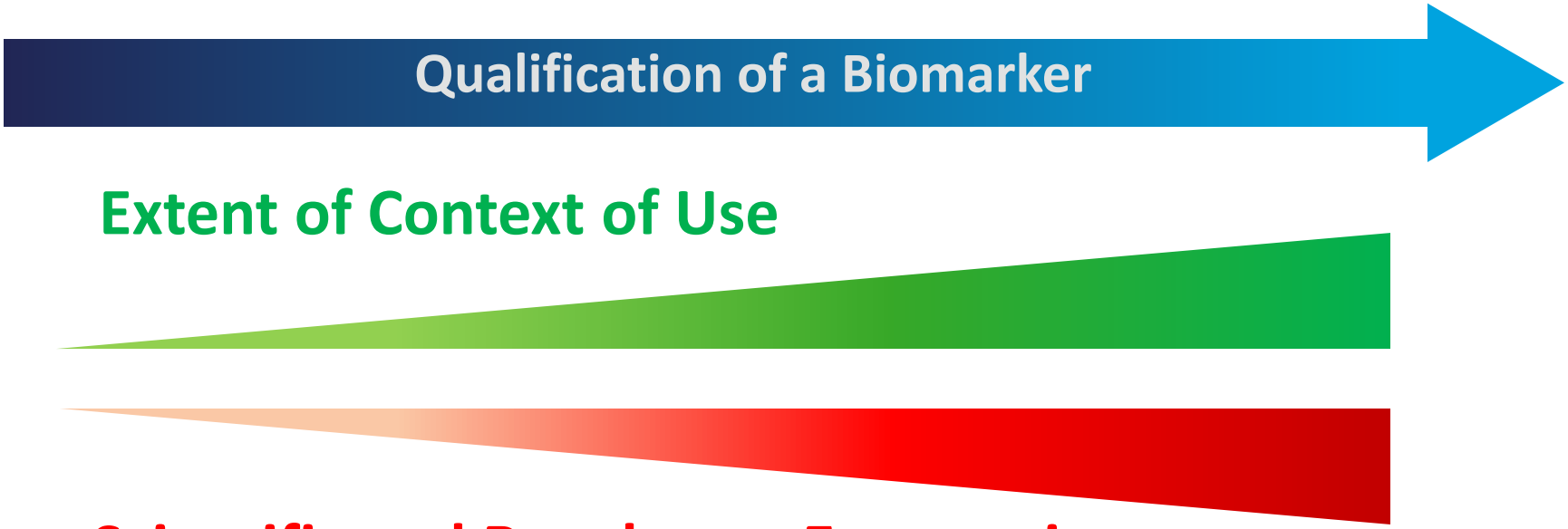

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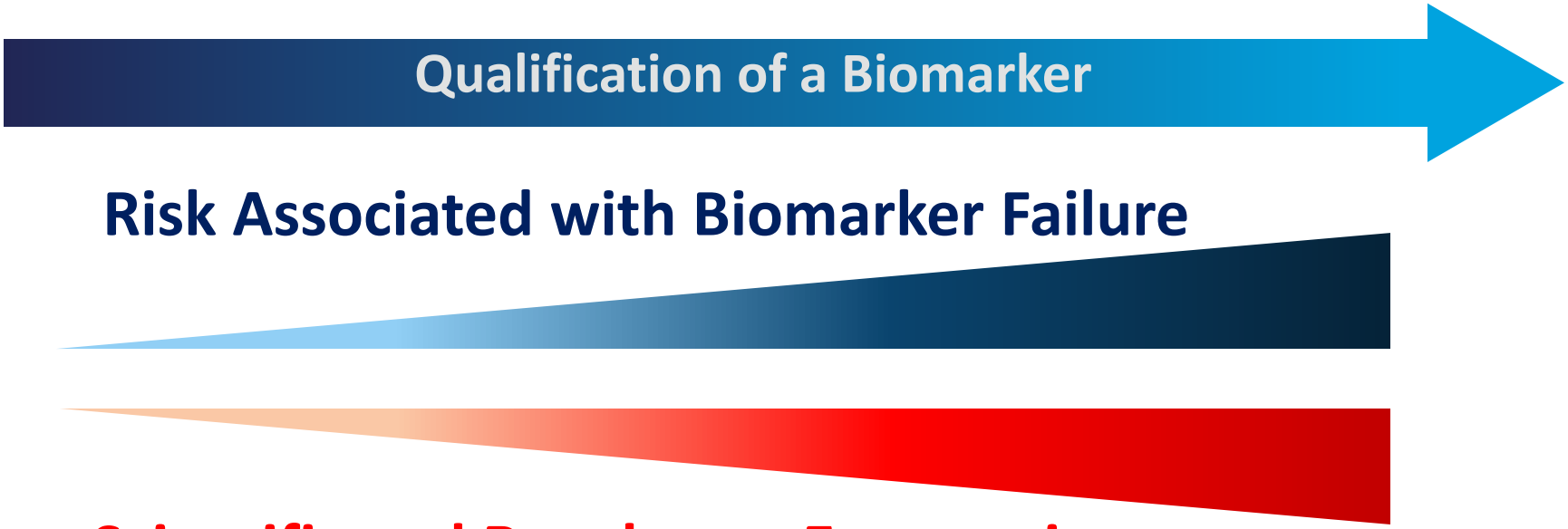


Drug Induced Pancreatic Injury

Two hypothetical Context of Use examples:

1. Broad COU – based on two prospective purpose-designed clinical trials with supporting nonclinical data

2. Limited COU – based on a prospective healthy volunteer study and a study in which patients were treated with a drug known to cause pancreatic injury with supporting nonclinical data

Drug Induced Pancreatic Injury

Hypothetical Example

In search for better biomarkers of drug-induced pancreatic injury:

The clinical diagnosis of drug induced pancreatic injury remains a challenge due to the lack of specific symptoms.

Amylase and lipase are the gold standard biomarkers for pancreatic injury.

- Amylase concentrations >3 times the upper reference limit indicates injury
- Lipase activities parallel the increased activities

Many conditions that might present with similar clinical symptoms are also associated with increased amylase and lipase concentrations.

Amylase and lipase are among the more poorly standardized tests in laboratory medicine.

Hypothetical biomarker panel for drug-induced pancreatic injury:

1. ~~MiR-216a~~
2. ~~MiR-375~~
3. Protein RA1609
4. Protein RT2864
5. ~~Trypsinogen-1~~
6. ~~Trypsinogen-2~~
7. Trypsinogen-3

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic injury:

Claim

Qualified pancreatic safety biomarkers are proposed to be used together with monitoring of conventional pancreas biomarkers (e.g., serum amylase and lipase), in early clinical drug development research to support conclusions as to whether a drug is likely or unlikely to have caused a mild injury response in the pancreas at the tested dose and duration.

Study Population

For use in healthy volunteers and patients with normal pancreatic function.

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic injury:

Implementation in Clinical Trial Design

1. Have **demonstrated the biomarkers responsiveness** to pancreatic injury in an animal toxicology study
2. Have shown evidence of mild pancreatic injury that is expected either not to be human relevant or to have a satisfactory safety margin over the targeted clinical therapeutic exposure
3. Have shown prior evidence in an animal toxicology study that pancreatic injury can be safely monitored

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic Injury:

Implementation in Clinical Trial Design

A human trial designed to evaluate safety of a drug may include qualified biomarkers (Serum RA1609, RT2864, and Trypsinogen-3):

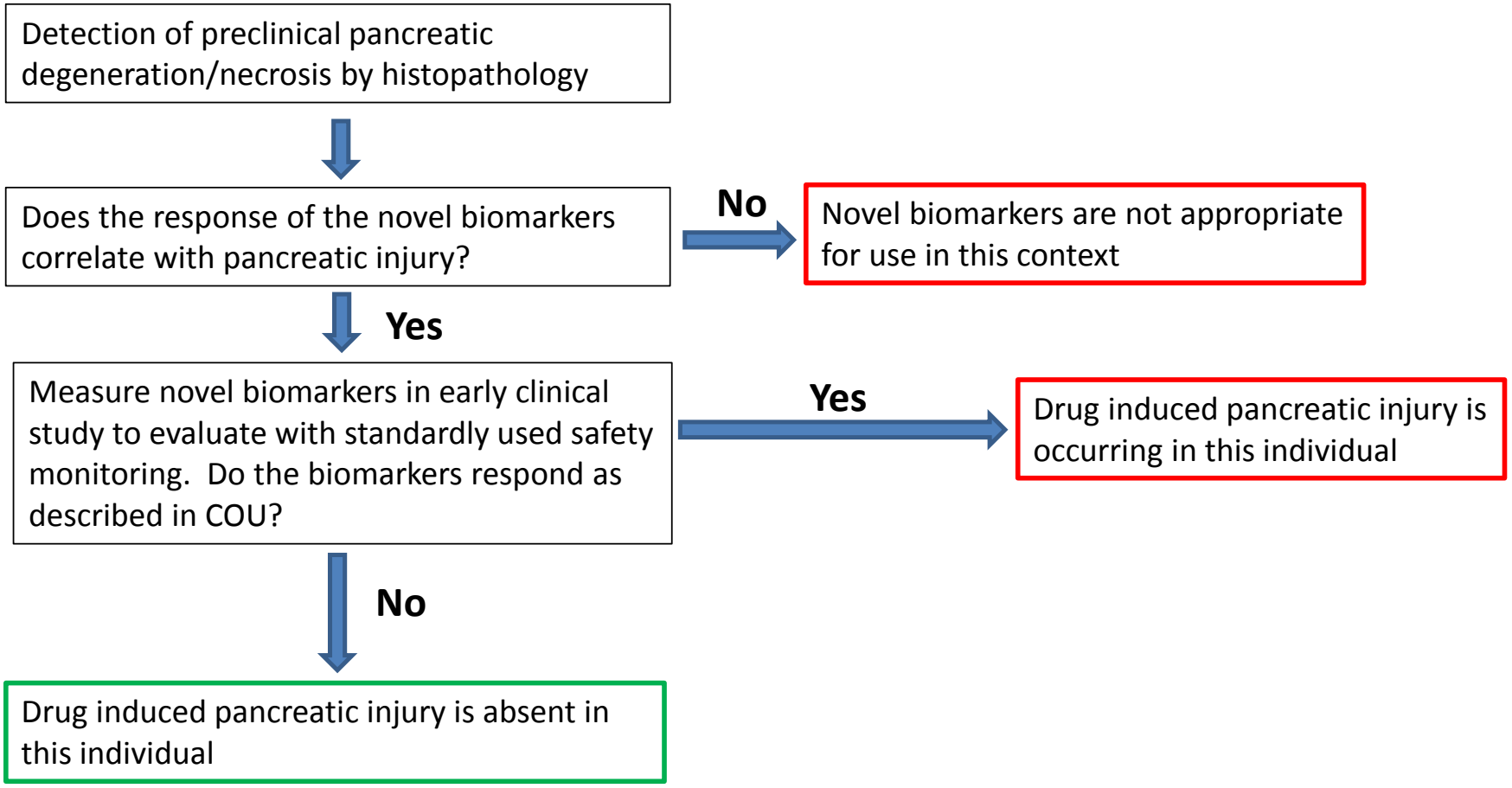
- For research use to make decisions in real time such that an **individual patient or an entire dose-cohort** of subjects may be triggered to stop or to pause dose escalation of a drug when a pre-specified biomarker threshold is exceeded.

- Change in biomarker serum concentrations as defined by **change from baseline** will enable the conclusion that a mild pancreatic injury response to a drug candidate was likely or not likely to have occurred in response to a drug in individual subjects.

- Biomarkers are intended to **complement the use of the standard biomarkers**, including lipase and amylase, and should be evaluated in conjunction with **standardly used safety monitoring**.

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic Injury:



PREDICTIVE ACCURACY

Nonclinical studies

Multiple studies (~*10*) with multiple pancreatic toxins (~*10*) primarily in the rodent with limited studies in canine and nonhuman primate

- ✓ **Correlation of biomarker response** to pathology and improved performance relative to other biomarkers
- ✓ **Biological understanding** and relevance to toxicity (**mechanism of response**)
- ✓ **Consistent response** across mechanistically different compounds, and similar response across sex, strain, and species
- ✓ Presence of **dose response and temporal relationship** to the magnitude of response
- ✓ **Specificity of response** to toxicity – understanding the response to toxicities in other tissues, or to pharmacologic effects without toxicity in the target organ

PREDICTIVE ACCURACY

Clinical studies

Two prospective studies in patients with currently used medications that have the potential to cause pancreatic injury.

- Azathioprine in Crohn's disease patients
- Mesalazine in ulcerative colitis patients with normal pancreas function

✓ Greater diagnostic predictivity compared to amylase and lipase as defined by:

1. A formal adjudication procedure
2. A predefined statistical evaluation

Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

What is the RISK if the biomarker lacks predictive accuracy?

Novel Safety Biomarkers

Lack of Predictive Accuracy

Safety of Individuals in Clinical Trials

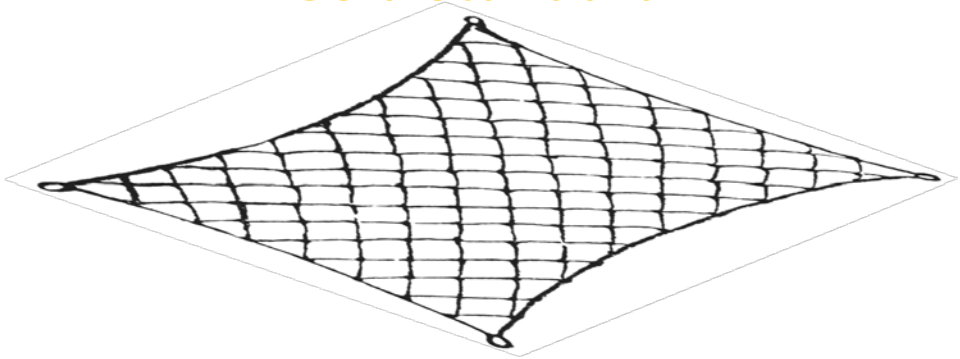
Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

What is the RISK if the biomarker lacks predictive accuracy?

Novel Safety Biomarkers

Gold Standard

Amylase



Lipase

Safety Net

Type I vs. Type II Error

Safety of Individuals in Clinical Trials

Additional areas of scientific expectation:

- Nonclinical and clinical data expectation for (translational) qualification of clinical safety biomarkers
- Biomarker assay validation and performance expectations
- Expectations around clinical data generation (how much rigor in study conduct?)
- Statistical methodology expectations for confirmatory data analysis
- Is there a need for prospective sample generation and analysis or can prospective analysis occur on previously obtained samples?

Drug Induced Pancreatic Injury

Two hypothetical Context of Use examples:

1. **Broad COU –** based on two prospective purpose designed clinical trials with supporting nonclinical data

2. **Limited COU –** based on a prospective healthy volunteer study and a study in which patients were treated with a drug known to cause pancreatic injury with supporting nonclinical data

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:

Claim

A Composite Measure (CM) of serum Protein RA1609, Protein RT2864, and Trypsinogen-3 is a qualified safety biomarker of pancreatic injury response for use in normal healthy volunteer trials supporting early drug development.

Study Population

For use in healthy volunteers only.

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic injury:

Implementation in Clinical Trial Design

1. **Have demonstrated the biomarkers responsiveness** to pancreatic injury in an animal toxicology study
2. Have shown evidence of mild pancreatic injury that is expected either not to be human relevant or to have a satisfactory safety margin over the targeted clinical therapeutic exposure
3. Have shown prior evidence in an animal toxicology study that pancreatic injury can be safely monitored

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:

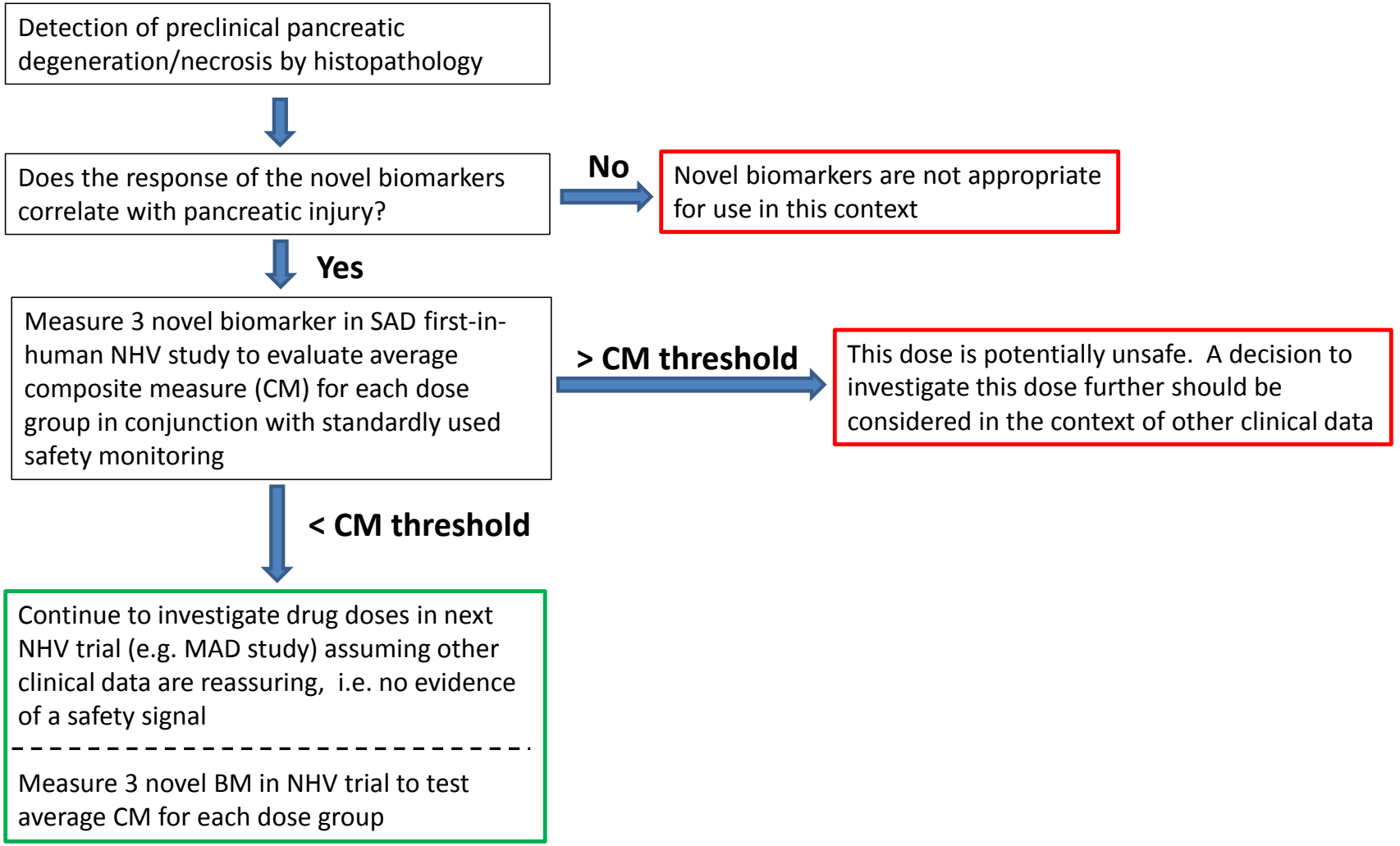
Implementation in Clinical Trial Design

A human trial designed to evaluate safety of a drug may include qualified biomarkers (Serum RA1609, RT2864, and Trypsinogen-3):

- The **CM is a measure of the of serum RA1609, RT2864, and Trypsinogen-3** expressed as fold change from baseline
- The group average CM is qualified for study Sponsors to determine if there is an increased likelihood of a pancreatic injury response for a dose of an investigational drug in a **dose cohort** when benchmarked to results provided herein for **normal healthy volunteers**
- The CM is **not qualified for individual subject safety monitoring**
- Biomarkers are intended to **complement the use of the standard biomarkers**, including lipase and amylase, and should be evaluated in conjunction with **standardly used safety monitoring**

Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:



Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 2

PREDICTIVE ACCURACY

Nonclinical studies

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PREDICTIVE ACCURACY

Clinical studies

One study in heathy subjects to define the variability associated with the biomarkers and one study with Crohn's disease patients treated with Azathioprine known to have pancreatic injury.

- ✓ Demonstrate that a Composite Measure of novel biomarkers can differentiate cohorts of heathy subjects experiencing drug-induced pancreatic injury from cohorts not experiencing injury.

Conclusions

We have defined two approaches to qualification of translational safety biomarkers and delineated some of the scientific expectations for these hypothetical projects

However, we must align and codify these expectations, as well as those in other areas:

- **Nonclinical and clinical data expectation for (translational) qualification of clinical safety biomarkers**
- **Biomarker assay validation and performance expectations**
- **Expectations around clinical data generation**
- **Statistical methodology expectations for confirmatory data analysis**

Thank You

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