Innovative strategies for fit-for-purpose RWE research:

Maximizing data completeness and accuracy

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Speakers

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Innovative strategies for fit-for-purpose RWE research:

Maximizing data completeness and accuracy

Today's agenda

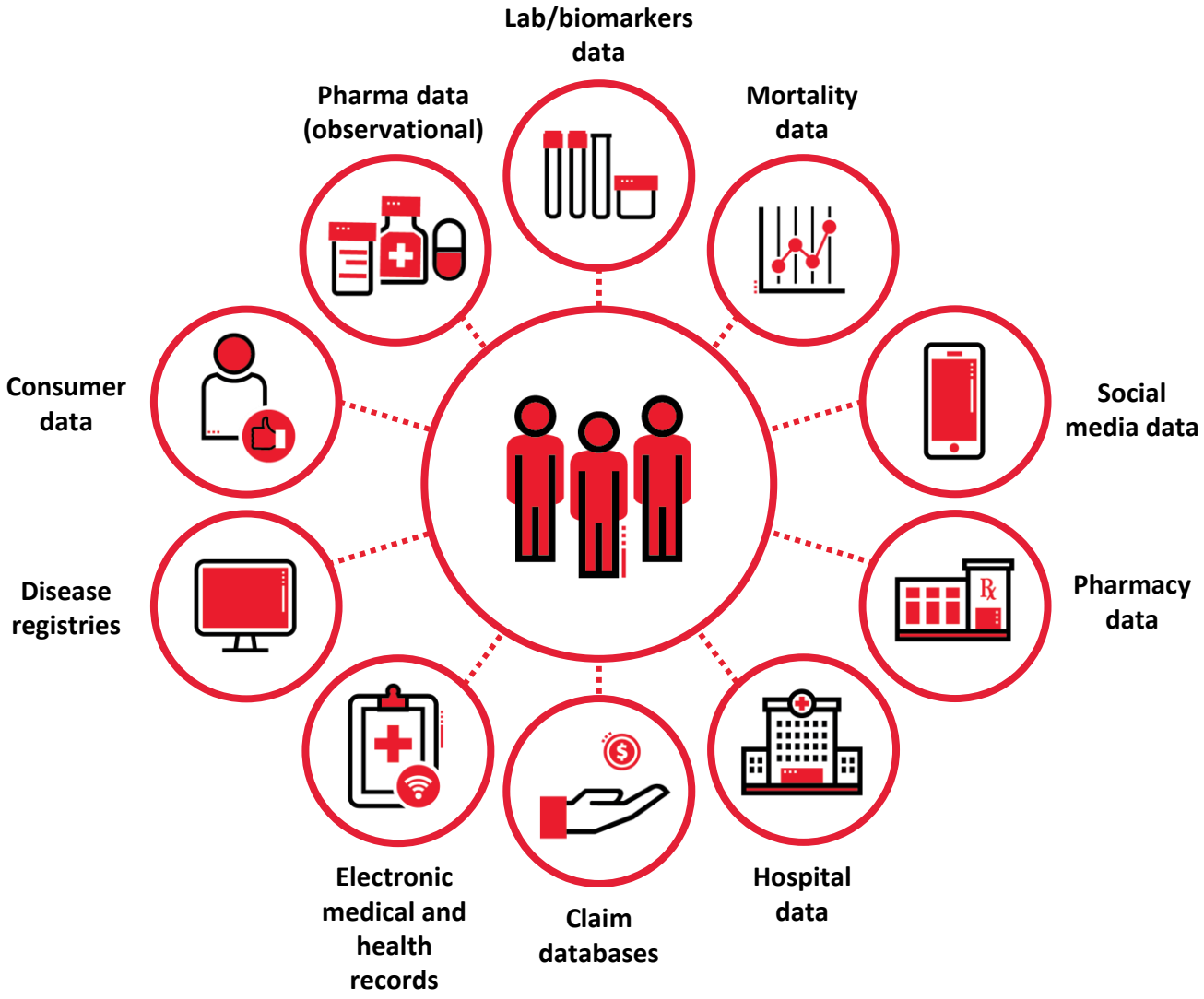
For the next 30 minutes

1. **Discuss common dataset challenges**
2. **Explore our novel physician-led chart abstraction methodology**
3. **Review successful RWE examples of data completeness and accuracy**
4. **Audience Q&A**

Dataset challenges

Common dataset challenges

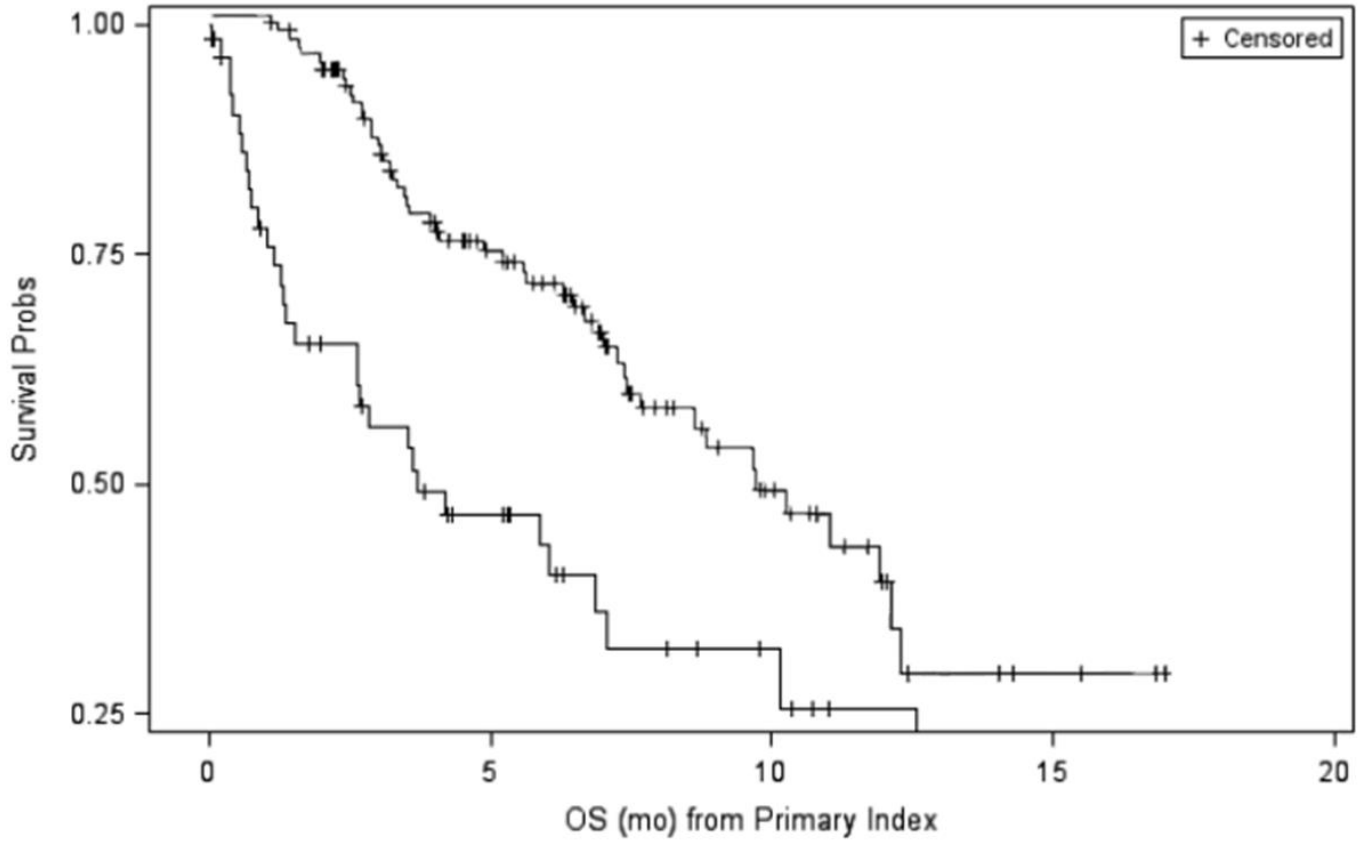
- Finding the patients
- Incomplete data
- Inaccurate data
- Misclassification of data
- Representativeness



Challenges lead to bias

How to spot bias in a Kaplan Meier Curve 101

- Flat line at top = **immortal time bias**
- Unequal number of censor points = **sample size problem**
- Large immediate gap = **selection bias**



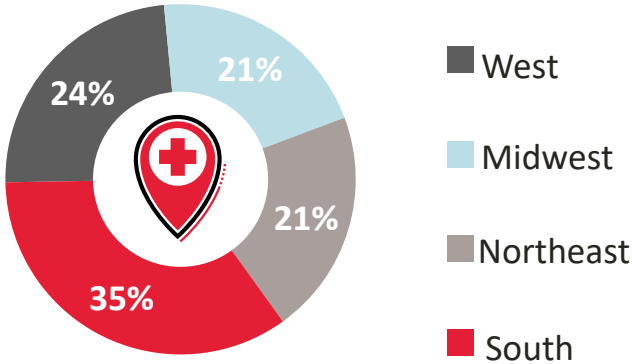
Source: Modified from Cardinal Health project data Kaplan Meier curve

Patient-level data from provider and practice research networks

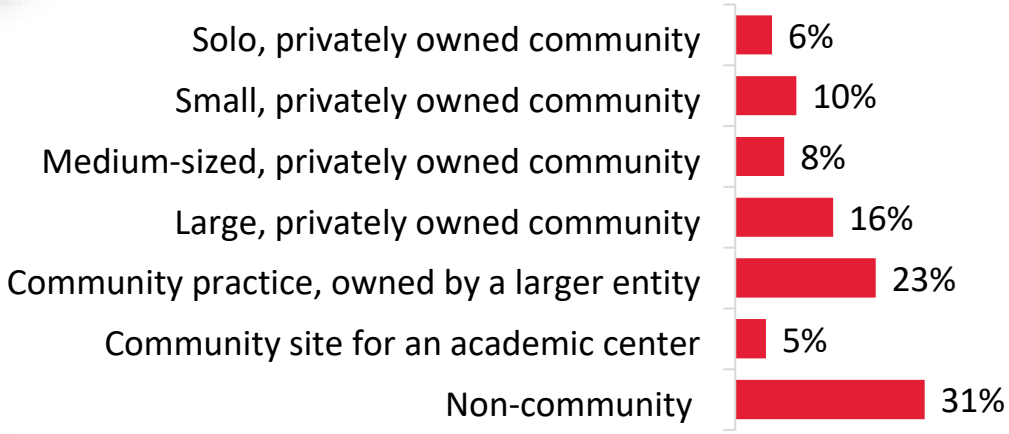
Oncology Provider Extended Network (OPEN)

More than 800 unique GPO- and EMR-agnostic OPEN providers

ACROSS ALL 50 STATES



REPRESENTATIVE PRACTICE SETTINGS



PHYSICIAN-LED CHART REVIEW PROCESS

- Physicians treating patients complete electronic case report forms (eCRFs) customized during study development
- Data QA/QC including provider training, UAT, query generation
- Up-to-date data; abstraction may occur using the most recent patient encounter

VARIABLES CAPTURED

- Patient/provider demographics, clinical characteristics, genomics and biomarkers
- Outcomes including disease specific measures (e.g. tumor response, disease activity scores)

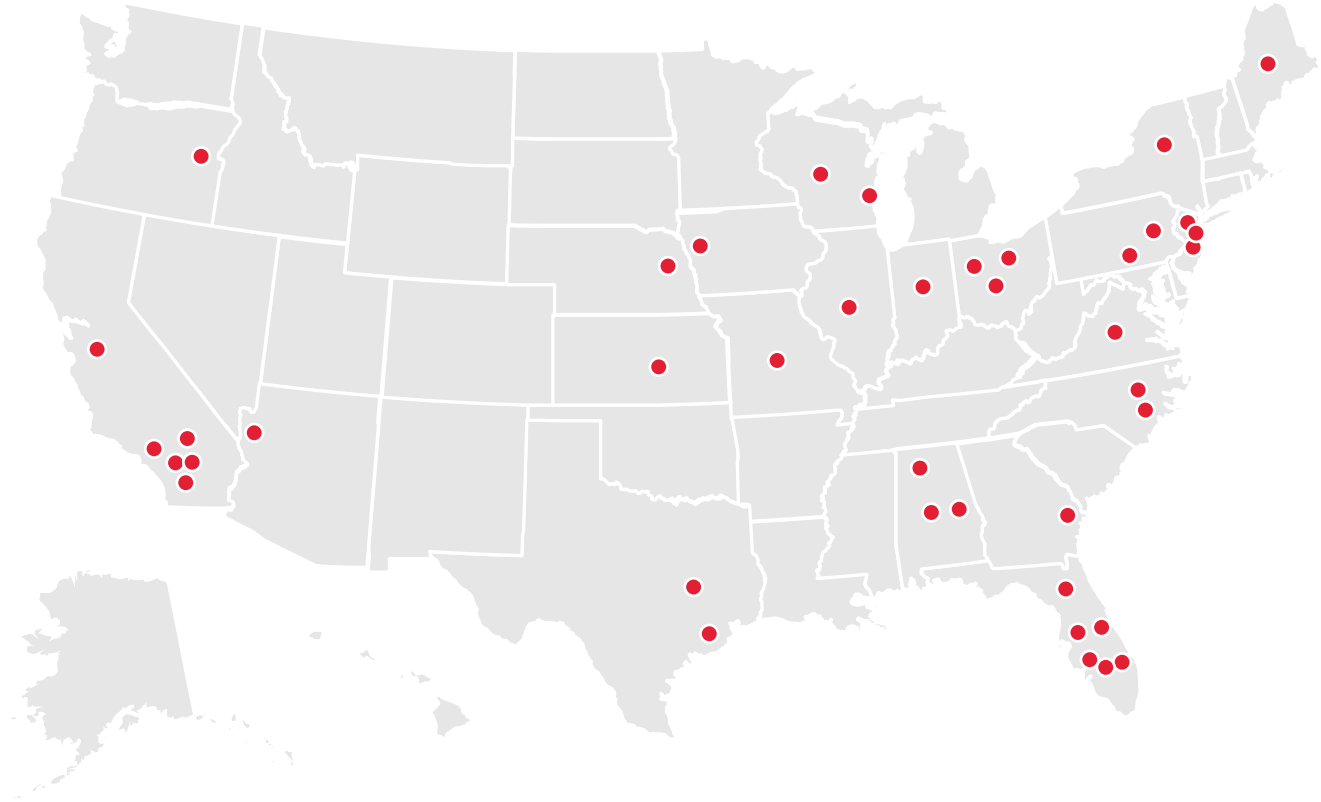
*Cardinal Health data as of 3/2024– Data available 2023-current

Practice Research Network (PRN)

- Link PRO data with clinical/EMR data
- Monitor adherence persistence and document barriers to care
- Collect prospective, longitudinal patient data
- Generate RWD and RWE to use in regulatory submissions

KEY

40 ONCOLOGY PRACTICES



Cardinal Health data as of 4/2024

Data completeness and accuracy

Hard-to-find variables captured in our dataset

Provider demographics	Years in practice, number of patients, specialty, sub-specialty, practice setting
Patient demographics	Year of birth, Race, ethnicity, sex, ECOG PS
Disease state specifics	Date diagnosed, extent, stage, grade
Efficacy assessments	Disease response
Toxicity assessments	Adverse event start and end date, severity
Therapeutics	What, when, how modified, duration, treatment regimen, line of therapy, dosage

Case study: Comparing demographic representativeness across RWE, trial data and registry data

Methodology

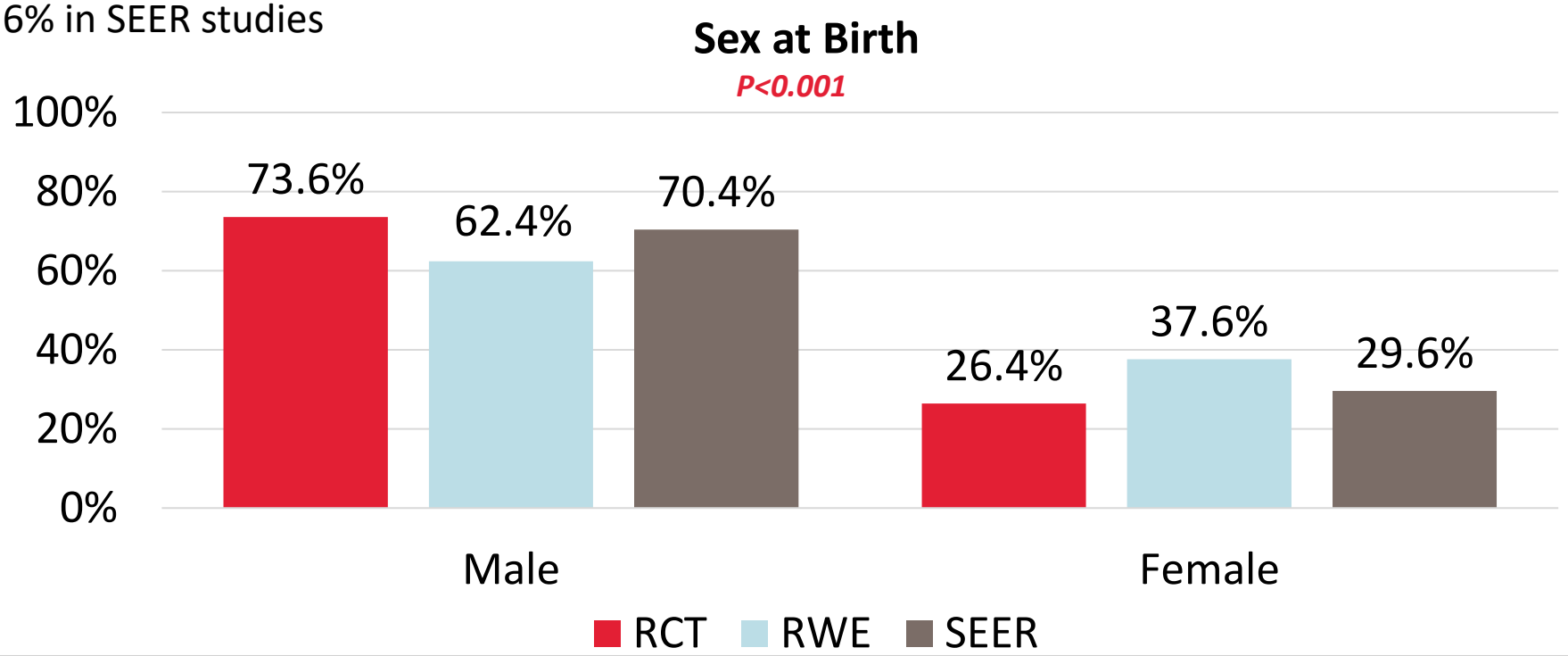
Studies included	Studied variables	Oncology areas
• Selected contemporaneous periods spanning 2017-2022 • Identified RWE studies conducted in Cardinal Health • Identified corresponding RCTs with similar inclusion/exclusion criteria; data extracted from clinicaltrials.gov • Included 7 double-blind oncology RWE studies and 9 RCTs • Used SEER data as a proxy for the U.S. population	• Age • Race • Ethnicity • Sex (among non-breast cancer studies)	• Breast cancer (2 RWE studies and 4 RCTs) • Advaned renal cell carcinoma (1 RWE studies and 2 RCTs) • Liver cancer (1 RWE study and 1 RCT) • NSCLC (2 RWE studies and 1 RCT) • Melanoma (1 RWE study and 1 RCT)

RWE= real-world evidence, RCT = randomized control trial, SEER =Surveillance, Epidemiology and End Results national cancer database

Sex at birth

Female representation was significantly higher in RWE (37.6%) vs. RCT (26.4%)

- Sex at birth was collected for 26,325 patients across 3 data sources:
  - RWE: n=2,120, 8.1%
  - RCT: n=3,962, 15.1%
  - SEER: n=20,238, 76.9%
- Aggregated across the populations studied, female representation was 37.6% in RWE, 26.4% in RCT, and 29.6% in SEER studies

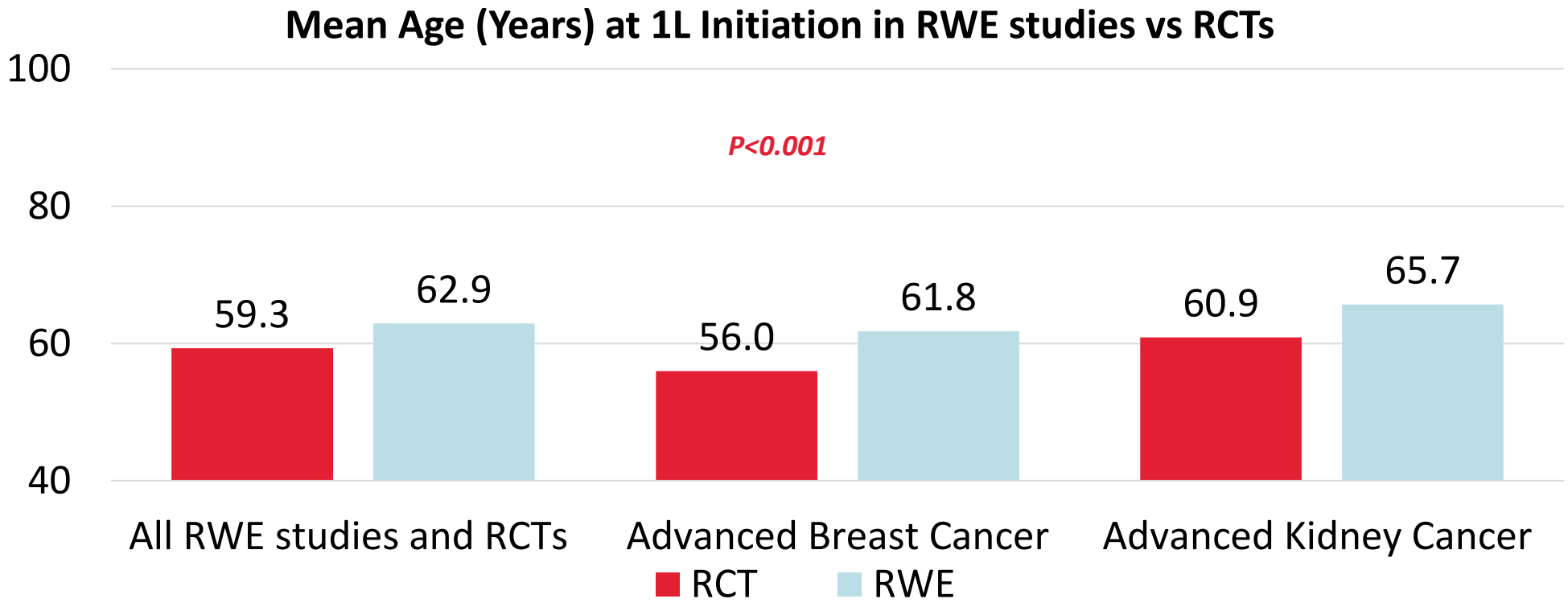


Age at first line treatment initiation

Patients in RCTs were significantly younger (56.0-60.9 yrs.) vs. RWE studies (61.8-65.7 yrs.)

In RWE studies, relative to RCTs:

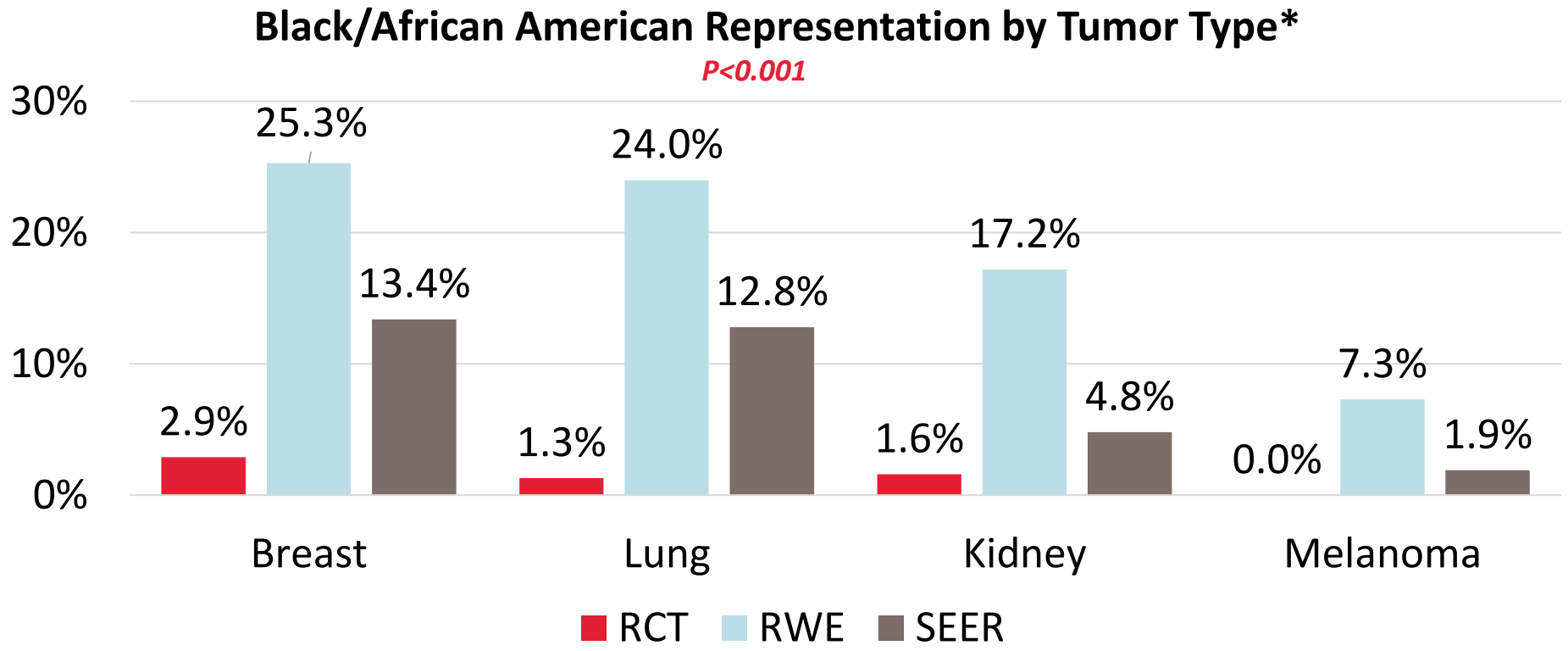
- Mean age at 1L initiation was significantly higher when comparing all seven RWE studies to all eight RCTs
- Mean age at 1L initiation was also significantly higher in specific comparisons of RWE studies to three breast cancer RCTs
- Mean age at 1L initiation was also significantly higher in specific comparisons of RWE studies to two kidney cancer RCTs



Race

A significantly higher percentage of patients were Black/African American in RWE (7.3%-25.3%) vs. RCTs (1.3-2.9%)

- Across advanced breast, lung, liver, kidney, or melanoma skin cancer studies, Black/African American race representation was highest in RWE and lowest in RCT studies
- Representation of Black/African Americans was 25% or less across data sources by tumor type.



*Reported in all RWE, RCT and SEER studies of advanced breast, lung, liver, kidney or melanoma skin cancer

Ethnicity

Hispanic patients were underrepresented in RCTs and the majority of RCTs did not report ethnicity at all

- Example in advanced renal cell carcinoma

Overall Hispanic Ethnicity Representation by Tumor Type			
N= 83,298	RWE: n(%) n = 2,980	RCT: n (%) n = 6,168	SEER: n(%) n = 74,150
Breast (N= 57,479) Hispanic ethnicity[1]	n= 860 96 (11.2)	n= 2,707 Not reported	n= 53,912 8,564 (15.9)
Lung (N=10,089) Hispanic ethnicity[1]	n= 783 84 (10.7)	n= 559 Not reported	n= 8,747 610 (7.0)
Liver (N=7,993) Hispanic ethnicity[1]	n=290 40 (13.8)	n=0 Trial not analyzed	n= 7,703 1,556 (20.2)
Advanced Renal Cell Carcinoma (N=4,821) Hispanic ethnicity[1]	n= 635 95 (15.0)	n= 1,957 66 (3.4)	n= 2,229 439 (19.7)
Skin melanoma (N=2920) Hispanic ethnicity[1]	n= 412 34 (8.3)	n= 945 Not reported	n= 1, 563 132 (8.4)

1. Reported in all RWE and SEER studies and 2 RCTs.

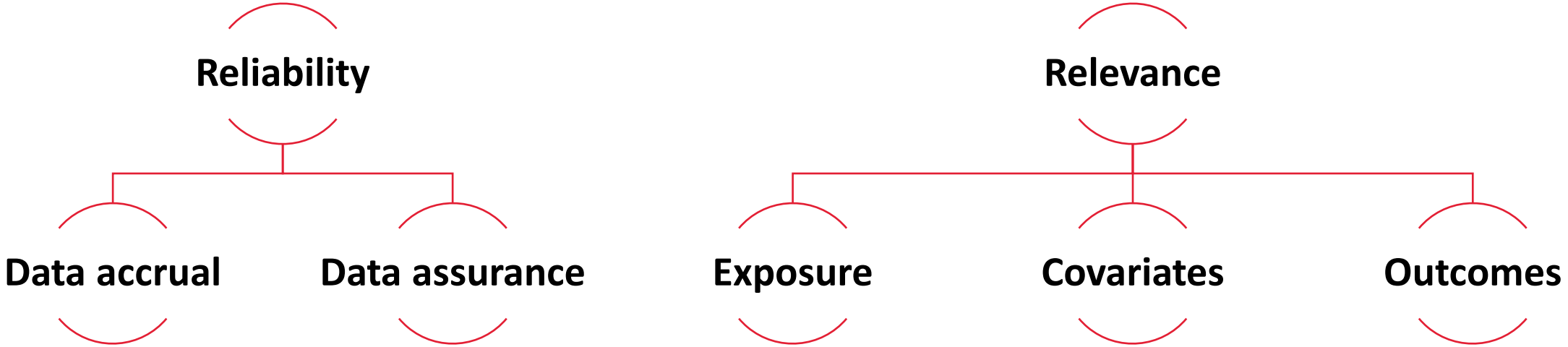
Oncology clinical decisions today are based on those who participated in clinical trials, only **3%** of the population

Source: ASCO Cancer-LINQ

Case study: Standardization in real-world study endpoints

Fit-for-purpose data considerations

Are the data suitable to address specific regulatory questions (fit for use) answered by the reliability and relevance?



Codes adequately represent the underlying medical concept

Relevant data captured/available

Source: Framework for FDA's Real-World Evidence Program

Addressing limitations of physician-charted responses in treatment outcome assessment using RWD

Claims/EMR study endpoints

- **Exposure based**
  - Treatment exposure
  - Time on treatment
  - Time to next treatment
- **Some adverse events**
  - Treated
  - Hospitalized
- **Survival (maybe)**

Chart review study endpoints

- **Exposure based**
  - Treatment exposure
  - Time on treatment
  - Time to next treatment
- **More adverse events**
  - Treated
  - Reported to physician
  - Hospitalized
- **Physician-charted response**
  - ORR, DoR, PFS, EFS
- **Survival (likely)**

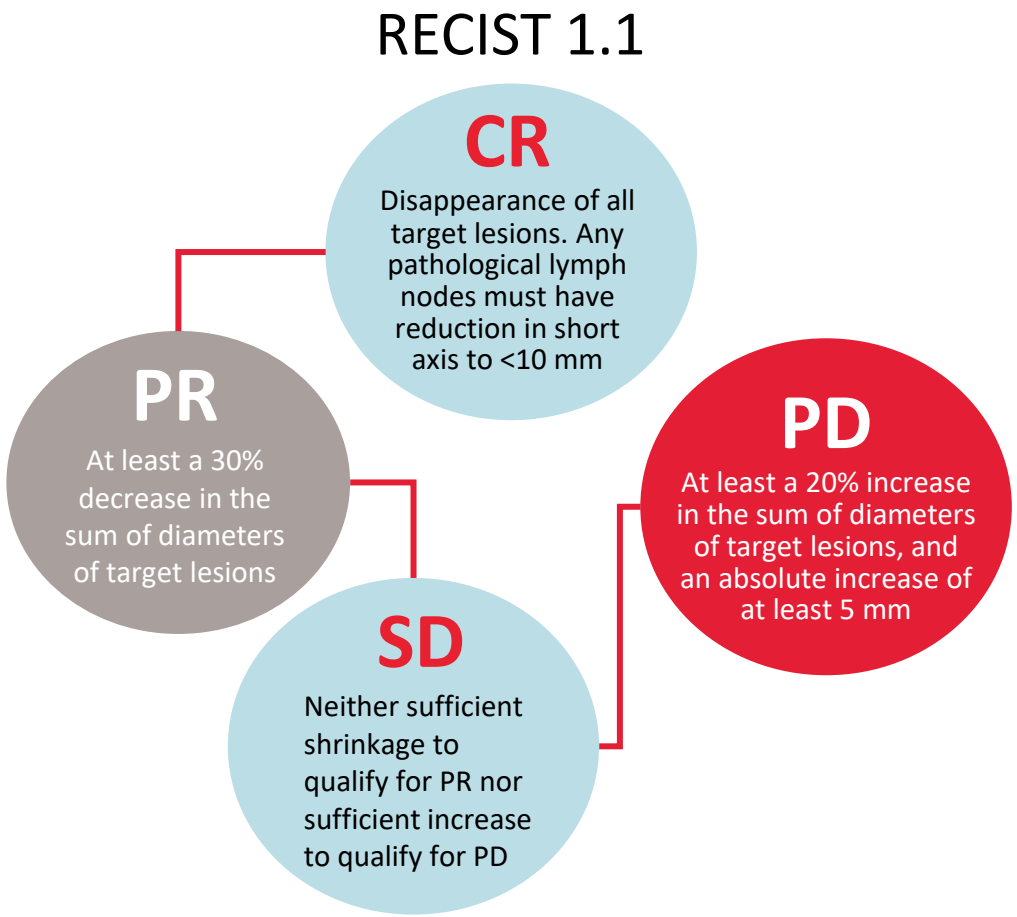
Clinical trial endpoints

- **Exposure based**
  - Intention to treat
  - Time on therapy
- **Most adverse events**
  - Treated
  - Reported to trial personnel
  - Hospitalized
- **BICR response (RECIST, Lugano, etc.)**
  - ORR, DoR, PFS, EFS
- **Survival**
  - Overall survival
  - Cause-specific survival

ORR= objective response rate, DoR = duration of response, PFS = progression-free survival, EFS = event-free survival, BICR = blinded independent central review

Blinded independent central review

The gold standard



Time point response: patients with target (+/-) non-target disease

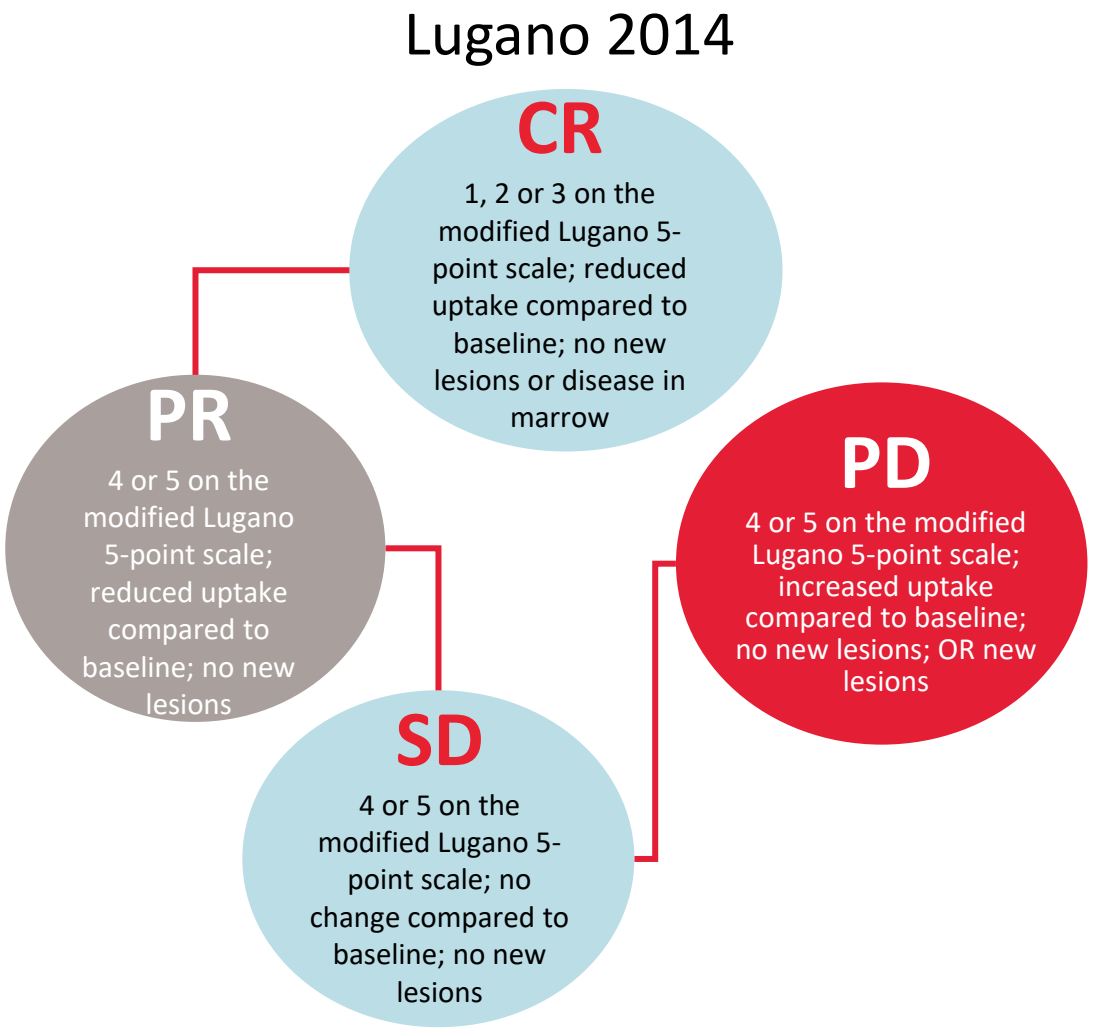
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluate	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR= complete response; PR = partial response, SD= stable disease; PD = progressive disease

Source: https://recist.eortc.org/recist-1-1-2/

Blinded independent central review

The gold standard



Modified Lugano 5-point scale	
Deauville Score	
Score	Description
1	No FDG uptake
2	FDG uptake ≤ mediastinum
3	FDG uptake > mediastinal but ≤ liver
4	FDG uptake > liver at any site
5	FDG uptake > liver and new sites of disease
X	New areas of FDG uptake unlikely to be related to lymphoma

CR= complete response; PR = partial response, SD= stable disease; PD = progressive disease

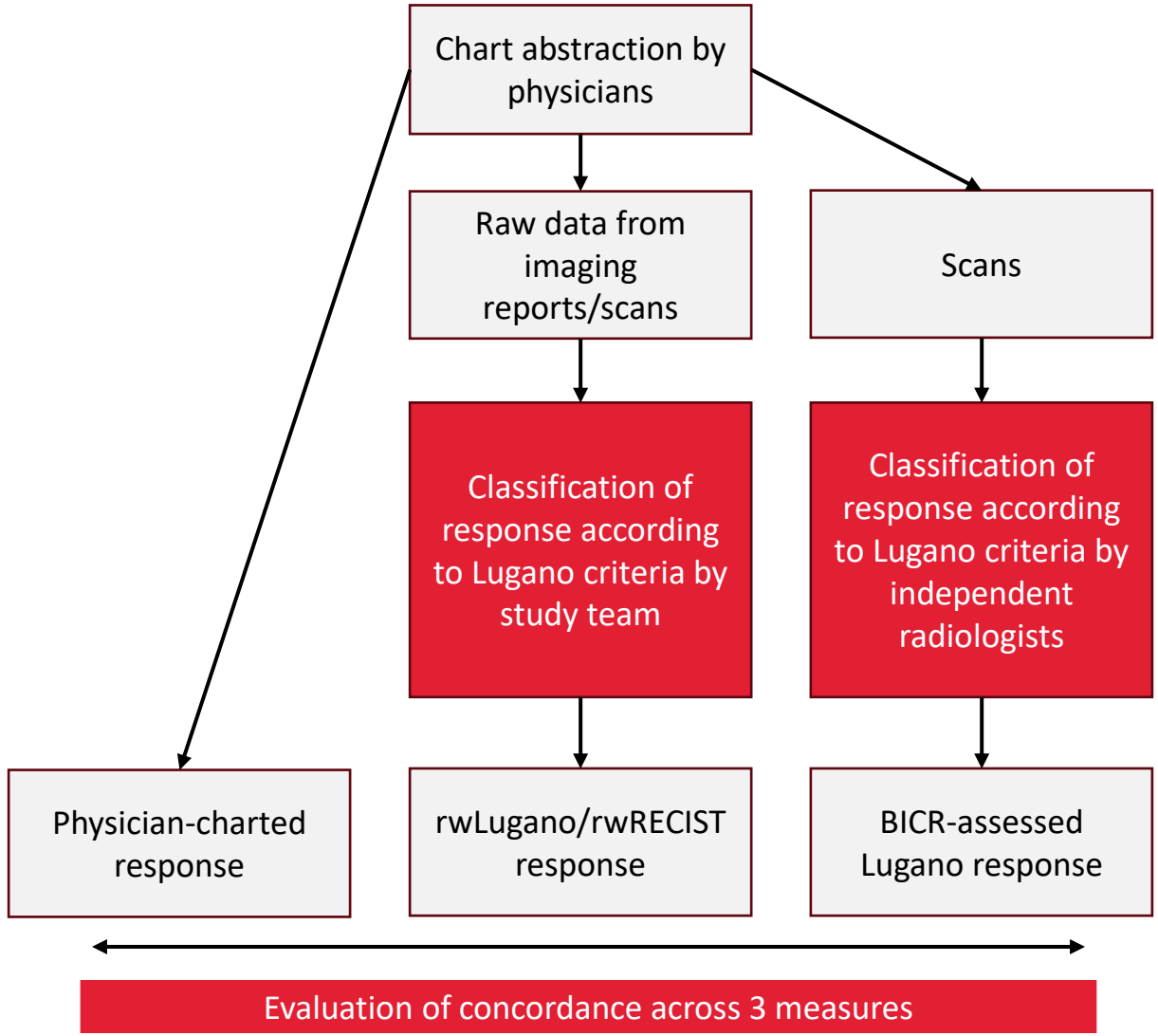
FDG =fluorodeoxyglucose

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5479259/

Standardizing in the real-world

rwLugano: an algorithm based on Lugano 2014 criteria used to derive treatment response in real-world data

rwRECIST: an algorithm based RECIST 1.1 criteria used to derive treatment response in real-world data



BICR= blinded independent central review; rwLugano= real-world Lugano; rwRECIST = real-world RECIST

rwRECIST and rwLugano advance the state of the art in outcome assessment using RWD

Improvement on real-world outcomes

Endpoints

Exposure-based real-world endpoints have limited association with clinical endpoints

Time

Blinded independent review is resource intensive and typically not feasible

Bias

Physician-charted response may be subjective

Standardization

Standardized approach reduces variability and misclassification

Importance of standardized approaches to oncology therapy response classification

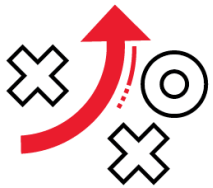
To maximize data completeness and accuracy…

Deep clinical data

Real-world evidence contributes meaningful data to clinical research

Representativeness

Benefits and limitations of data sources whether clinical trial, registry or real-world data must be considered when drawing conclusions



Standardized endpoints

Standardized RWD endpoints, such as rwRECIST and rwLugano, increase comparability of findings between studies

Questions?

For more information, visit us at booth 307 or email us at biopharmasolutions@cardinalhealth.com