# Practical Considerations for External Control Arm

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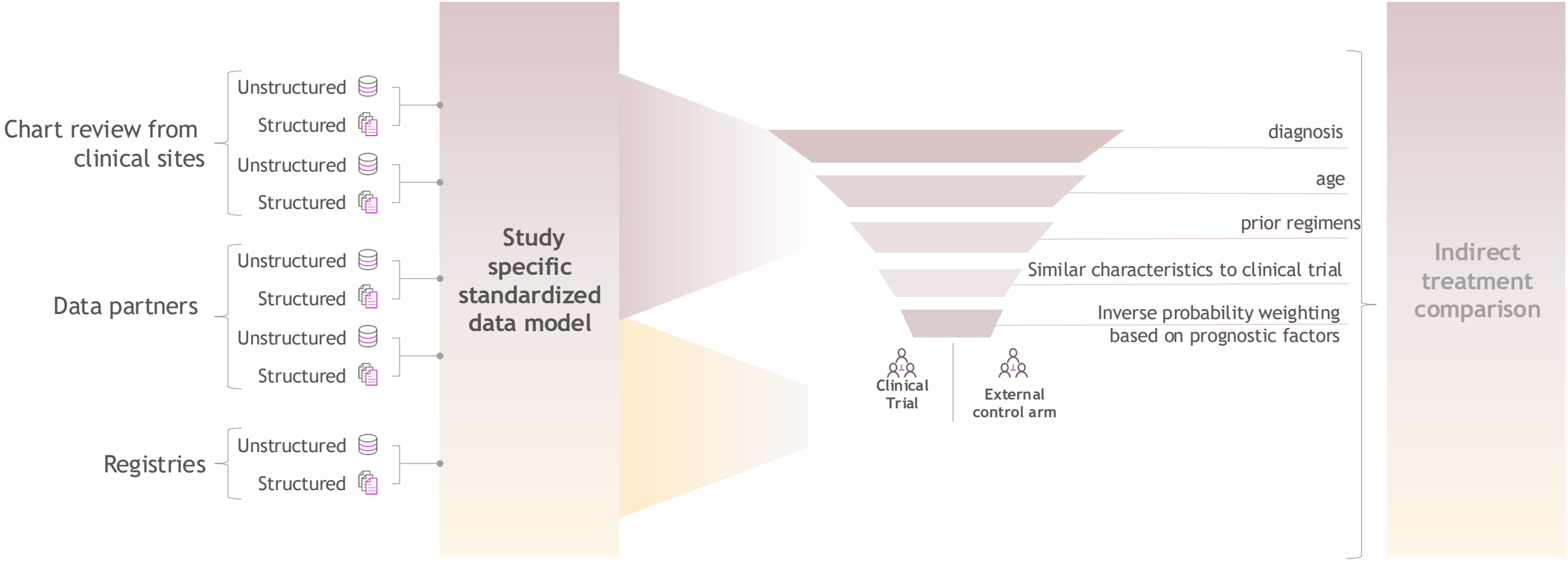
# Case example:
# Establishing an external control arm in supporting clinical trials

**Data acquisition** → **Data integration & harmonization** → **Trial specific dataset**



# Practical considerations for ECA

## 1. Identify RWD sources for the patient population of interest

| | Registries | Electronic medical records | Chart review |
|---|---|---|---|
| **Pros** | • Large sample size<br>• Longitudinal follow up<br>• Standardized data collection<br>• Diverse patient population | • Rich clinical detail<br>• Large sample size<br>• Comprehensive patient characteristics and outcomes<br>• Link to lab results and imaging | • Tailored to research question<br>• Specific clinical information<br>• Targeted data collection<br>• Capture nuanced clinical decisions and patient outcomes |
| **Cons** | • Selection bias<br>• Limited to variables collected<br>• May lack detailed clinical information<br>• Missing data | • Inconsistencies in documentation<br>• Unstructured data requires significant preprocessing<br>• Data harmonization can be complex<br>• Missing data | • Time-consuming and labor-intensive<br>• Smaller sample size<br>• Requires access to clinical sites and patient consent<br>• May not represent broader population |

## Consideration:

- Utility of different sources of RWD and prospective and retrospective data

# Practical considerations for ECA

## 2. Run quality and feasibility assessment in identified RWDs

- **Sample size**
  - Adequate power – merge RWDs if necessary
  - Representativeness
  - Subgroup analysis
- **Endpoints of interest**
  - Alignment with trial endpoints
  - Consistency in definitions
  - Data quality
- **Patient and disease characteristics**
  - Demographics and medical history
  - Disease stage/severity and comorbidities
  - Labs and imaging

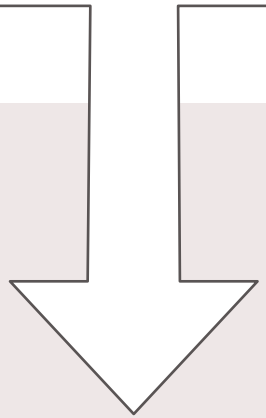
## Consideration:

1. Quality, currentness, and population representativeness of RWD
2. Combination of different RWD sources in terms of potential variability in the variable definition

# Practical considerations for ECA

**3. Identify and rank clinically relevant prognostic factors for indirect treatment comparison**

- **Systematic literature review** (SLR)
- **Clinical input** (expert panel, present SLR findings, clinical relevance assessment)
- **Statistical methods** (statistical significance and effect size in predicting clinical outcomes)



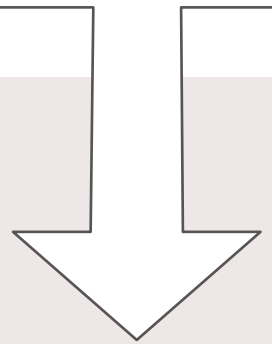
**Consideration:**

Identifying, ranking, and selecting prognostic factors of interest in determining propensity score to balance for external control arm purposes

# Practical considerations for ECA

## 4. Handle missing data

- Exclude variables with high percentage missingness to avoid bias
- Impute missing values with multiple imputation to enhance data completeness



**Consideration:**

Implications of missing data from the identified RWD sources and approaches to address potential concerns regarding missing data?

# Practical considerations for ECA

## 5. Run indirect treatment comparison

| | Inverse probability of treatment weighting (IPTW) | Propensity score (PS) matching | Doubly robust estimation (PS methods + outcome regression) |
|---|---|---|---|
| **Pros** | • Utilizes all data<br>• Can handle many covariates and complex relationship | • Mimics randomization<br>• Can handle many covariates and complex relationship | • Provides consistent estimates if either the PS model or the outcome model is correctly specified, offering protection against model misspecification. |
| **Cons** | • Sensitive to extreme weights, may requires weight truncation/ normalization<br>• Relies on correct specification of PS model | • Reduction in sample size, challenging for small datasets<br>• Relies on correct specification of PS model | • Requires correct specification of at least one of the models.<br>• Results can be more difficult to interpret |

## Consideration:

- IPTW, PS matching and doubly robust estimation as appropriate approaches to individual patient data (IPD)-to-IPD comparisons for external control arm purposes

# Thank you

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