Key Considerations in Using Real-World Evidence to Support Drug Development

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Contents

- **Development of Regulatory guidance and activities**
- Guidance of RWE and RWD issued by NMPA
- Visions

Milestones of RWE & RWD

2016
Sec. 3022. RWE in 21st Century Cures Act

2017
Guidance of RWE for medical devices (FDA, final)

2018
RWE Framework Program (FDA, final)

2019
Submitting Documents using RWD and RWE to FDA (FDA, draft)

2020
Guidance of RWE, final (NMPA, 2020.01.07)
Guidance of RWD, draft (NMPA, 2020.08.13)

2021
Deadline of Guidance of RWE for industry

Development of Regulatory Guidance and Activities

- **FDA**
  - Guidance
  - RCT Duplicate project, www.rctduplicate.org
- **EMA**
  - GetReal Initiative
  - Adaptive Licensing Pilot, 2014
  - HMA/EMA Task Force on Big Data
- **PMDA**
  - Guideline on pharmacoepidemiological study for drug safety assessment based on medical information database, 2014
  - Basic principles on the utilization of health information databases for post-marketing surveillance of medical products, 2017
- **ICH**
  - Pharmacoepidemiology Discussion Group (PEpiDG)

- **NMPA**
  - **Key Considerations in Using Real-World Evidence to Support Drug Development (Draft), May 2019**
    - Received 400+ comments from PhRMA, EFPIA, BIO, IFPMA, JPMA, ISPE, RDPAC, some hospitals, pharma companies, data companies and individuals.
  - **Guideline on Using Real World Evidence to Support Drug Development and Regulatory Decision-making (Implementation for trial), Jan 2020**
  - **Guideline on Real World Data Used to Generate Real World Evidence (Draft), Aug 2020**
  - **Guideline on Real World Study Used to Support Pediatric Drug Development and Regulatory Decision-making (Final), Aug 2020**

Contents

- Development of Regulatory guidance and activities
- **Guidance of RWE and RWD issued by NMPA**
  - Definition
  - RWD
  - RWE application scenarios
  - Design
  - Common statistical methods
  - Evaluation of RWE
  - Communication with the regulatory agency
  - Case study
- Visions

Definition of RWD/RWE/RWS

Real-World Data(RWD)

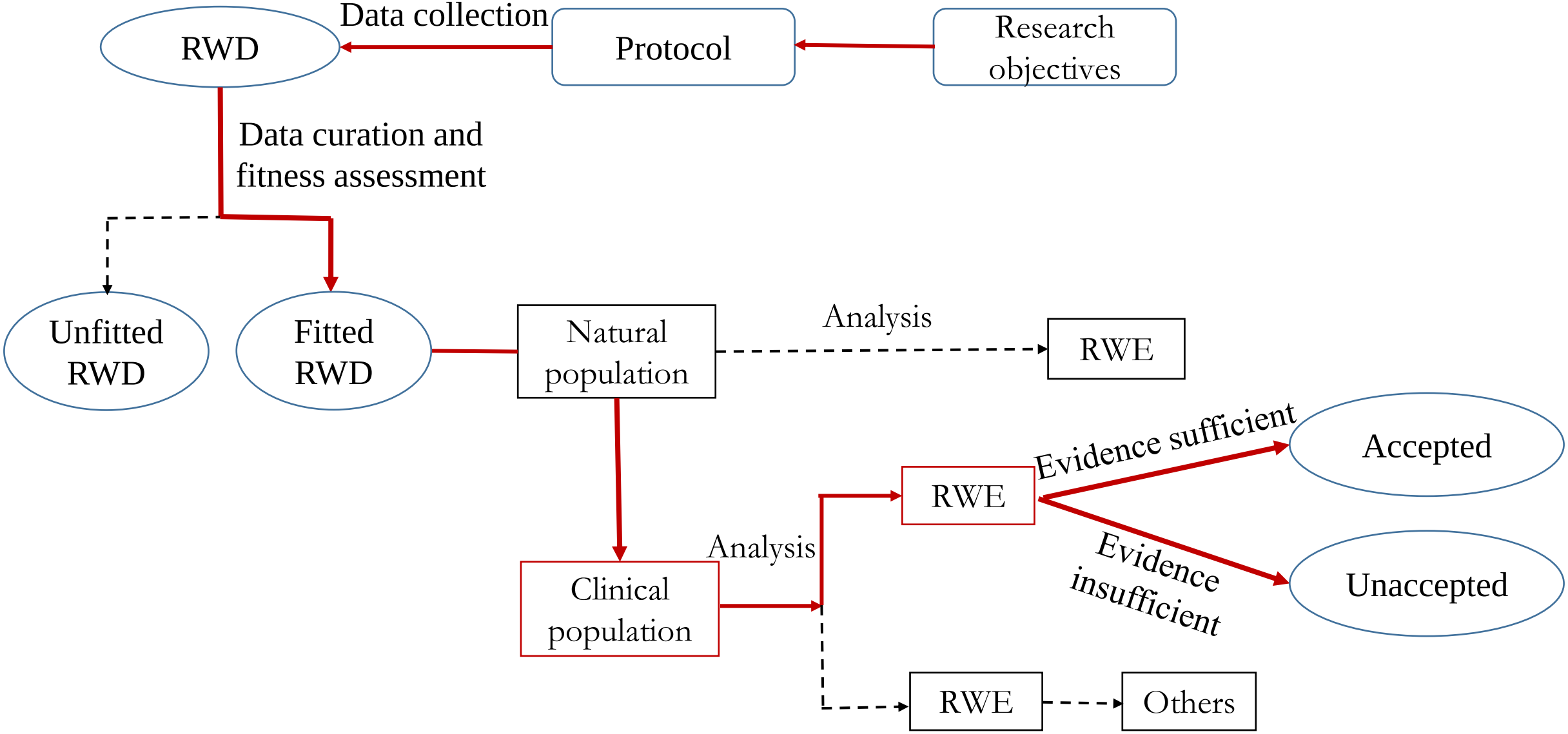
Real-world data (RWD) refer to a variety of data, collected on a daily basis, which are related to the patient's health status and/or diagnosis and healthcare processes.

Real-World Evidence (RWE)

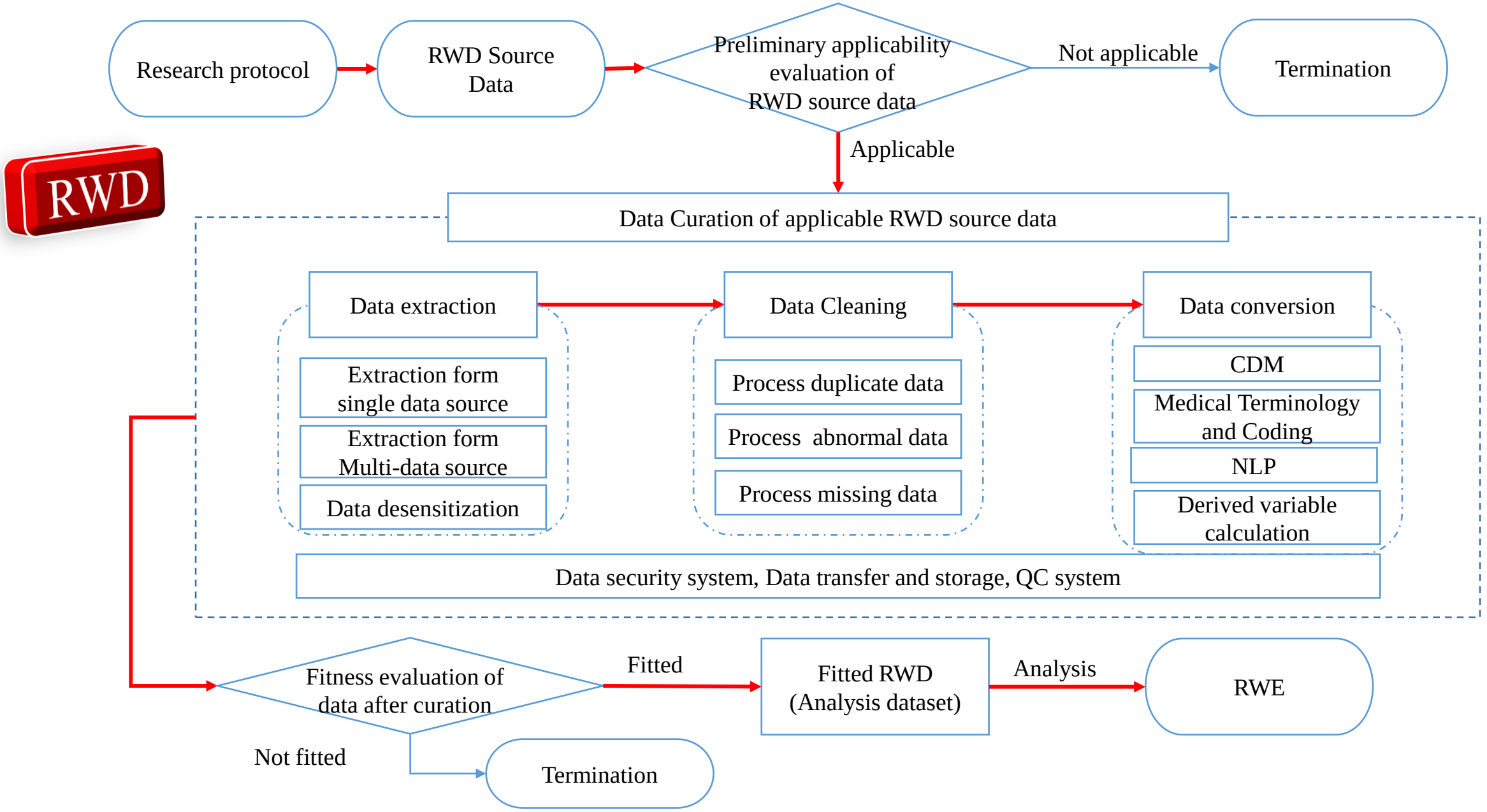
Real-World Evidence (RWE) refers to the clinical evidence on the use and potential benefit-risk of a drug, obtained through adequate and sufficient analysis of fit-for-purpose RWD. RWE includes evidence from retrospective or prospective observational studies, or interventional studies such as pragmatic clinical trials.

Real-World Study/Research (RWS/RWR)

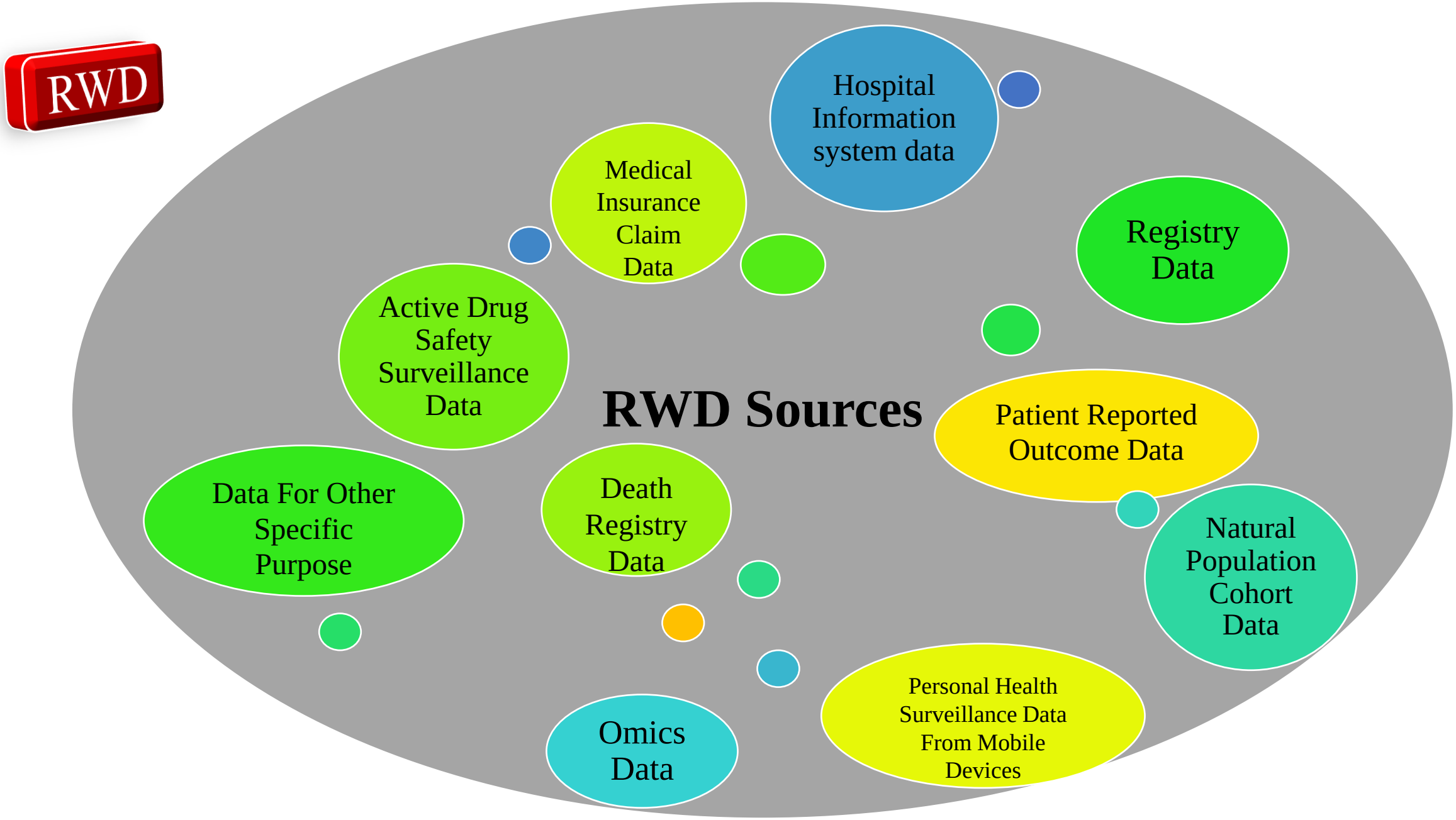
A process of, based on preset clinical questions, collecting data related to the health status and/or the diagnosis and treatment of research subjects in a real-world setting (ie, the real-world data) or utilizing the summary derived from the RWD, through analyses, to obtain clinical evidence of the drug usage and their potential benefit-risk (ie, the real-world evidence).



Pathways for RWS to support drug regulatory decision making (red solid line)



Fitness evaluation and data curation process of RWD for retrospective RWS



NMPA CDE-Guideline on Using Real-World Data to Generate Real-World Evidence (Draft for Public Review)

RWD Quality Evaluation

Fitness (fit-for-purpose)

Relevance

- Inclusion of important variables and information related to clinical outcomes；
- Definition of clinical outcome is accurate and the corresponding clinical meaning is clear
- Patients in the RWD are representative of the target population of the study
- Sufficient sample size and follow-up duration

Reliability

- Completeness
- Accrucy
- Transparency
- Quality Assurance

NMPA Guideline on Using Real World Evidence to Support Drug Development and Decision-making (Implementation for trial)

Application Scenarios of RWE

- Provide Efficacy and Safety Evidence to Support the Registration of New Drugs
- Provide Evidence for Label Modifications to Marketed Drugs
- Provide Evidence for Post-marketing Requirements or Drug Re-evaluation
- Summary and Clinical Development of Distinguished Veteran Traditional Chinese Medicine Doctors' Experience Prescription and Traditional Chinese Medicine Preparation from Medical Institutions
- Other Applications to Support Regulatory Decision Making

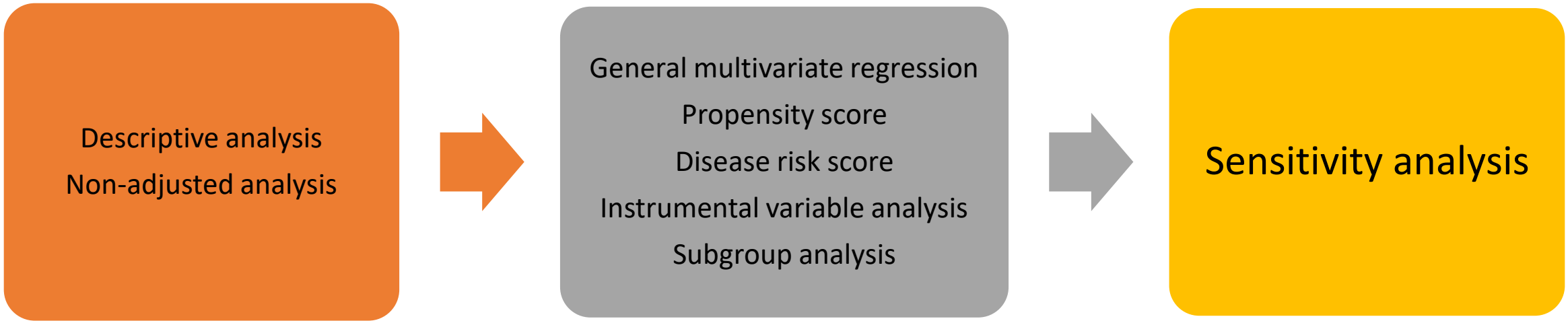
NMPA Guideline on Using Real-World Evidence to Support Drug Development and Regulatory Evaluation (For Trial Implementation)

RWE Study Design

- Single arm trial using external control (RWE)
- Pragmatic clinical trial (PCT)
- Observation study

  AHRQ. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide (2013) was recommended as a good reference

Common statistical methods in real world study



Evaluation of Real-World Evidence (1/2)

- Real-world Evidence and the Clinical Questions it Supports
  - What is the clinical question of interest to be answered?
  - Whether the use of RWE can answer the clinical questions of interest?
    - Scientific validity (e.g., with interpretable results, reasonable assumptions, well controlled type I error, etc.)
    - Regulatory requirements (potential conflict with other regulatory requirements, regulatory requirement for special disease areas, etc.)
    - Ethical considerations (ethical issues without using RWE?)
    - Operational feasibility (e.g., an independent statistician to ensure blinding and avoid bias during matching; any other operational challenges, etc.).

Evaluation of Real-World Evidence (2/2)

➢Transform Real-world Data to Real-world Evidence

- The research environment and data acquisition need to be close to the real world, such as a more representative target population, diversity of interventions compatible with clinical practice, or natural selection of interventions;
- Use of appropriate controls;
- More comprehensive evaluation of drug effectiveness;
- Effective bias control, such as the use of randomization, harmonization of measurement and evaluation methods, etc.;
- Appropriate statistical analyses, such as the correct use of causal inference methods, reasonable handling of missing data, adequate and sufficient sensitivity analyses, etc.;
- The transparency and reproducibility of evidence;
- Reasonable interpretation of results;
- Consensus among the relevant parties.

Communication with the regulatory agency

- **Scope :** Any use of real-world evidence for the purpose of drug registration
- **Content:**
  - ➢IND
    - Study objectives, Feasibility of using real-world evidence, RWD sources, Data curation plan, Data analysis methods;
    - Need to reach consensus on the use of RWE and conduct of RWR.
  - ➢Pre-NDA
    - Study implementation status, results and conclusions, NDA requirements.

Case study

➢Use real-world evidence to support extended drug combination

Evaluate the effectiveness and safety of bevacizumab in combination with platinum-based chemotherapy

- A vascular endothelial growth factor (VEGF) humanized monoclonal antibody
- In 2015, it was approved in China for combination with chemotherapy (carboplatin and paclitaxel) for the first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.
- Real-world use of chemotherapy with bevacizumab is not limited to carboplatin and paclitaxel.
- In October 2018, the drug was approved to extend the treatment regimen to a combination with platinum-based chemotherapy, based on the strong supporting evidence from three real-world studies.
- Combination of bevacizumab with platinum-based chemotherapy significantly prolonged PFS and OS compared with chemotherapy alone, consistent with global population data, and no new safety issues have been found.

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- RWE and RCT evidence both support regulatory decision-making. The strength of evidences from RWE, RCT or both of them is depended on their roles played on the chain of evidences.
- Three crucial elements of real-world study:
  - Fitted RWD
  - Good design
  - Proper analysis
- Bias of selected data must be avoided.

- **Current Challenges Of Using RWD in China**
  - Data infrastructure needs more concern
  - Data standards need to be unified
  - Policy barriers to data sharing need to be cleared
  - Data quality needs to be improved
  - Data curation technology needs to be standardized
  - Multidisciplinary collaboration mechanism needs to be strengthened

Acknowledgement

I would like to acknowledge Dr. Jun Wang from the Center for Drug Evaluation, NMPA, one of two key authors of “Guiddline on Using Real World Evidence to Support Drug Development and Decision-making” and “Guideline on Real World Data Used to Generate Real World Evidence” delivered by NMPA in 2020, who gave me a lot of constructive suggestions and shared his insightful views and ideas with me in preparing this PPT

Q & A

Q: Can you share the thinking regarding the decision for the China approval of Avastin in combination with platinum-based chemotherapy using 3 real-world studies?

A:

- Bevacizumab was approved in combination with chemotherapy (carboplatin or paclitaxel) in China.
- Off-label use of platinum-based chemotherapy with bevacizumab is a common phenomenon in the real-world setting.
- RWE generated from three real-world studies. These studies retrospectively analyzed patient data from three hospitals and showed that the combination of bevacizumab with platinum-based chemotherapy significantly prolonged PFS and OS compared with chemotherapy alone, consistent with global population data without new safety issues. In addition, related real-world studies have also provided data in different patient subgroups such as those with EGFR mutations or brain metastases, confirming the effectiveness and safety of bevacizumab combination therapy from multiple perspectives.

Thank you!

NMPA: Guideline on Using Real World Evidence to Support Drug Development and Decision-making (Implementation for trial)

NMPA: Guideline on Using Real-World Data to Generate Real-World Evidence(Draft for Public Review)