What You Need to Know About Drug Safety: Reporting Adverse Events in Clinical Trials vs the Real-World Setting

AMGEN® NOVARTIS

USA-334-83484

Important Information

This program is being presented on behalf of Amgen and Novartis, the sponsors of this program, and is being presented in accordance with the companies' compliance programs as well as FDA regulations

Program objectives

After this symposium, **participants will better understand the following**:

- Considerations for reporting adverse events (AEs) in the real-world setting and how these may differ from AEs in clinical trials
- Challenges in assessing causality between reported AEs in the real-world setting and the drug
- Post-approval AE reporting requirements outlined by regulatory agencies such as the FDA
- Implementation of safety signal management strategies by drug manufacturers
- Role of healthcare providers in reporting observed AEs outside of clinical trials

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How would you rate your current knowledge of the adverse event reporting process in clinical trials vs the real-world setting?

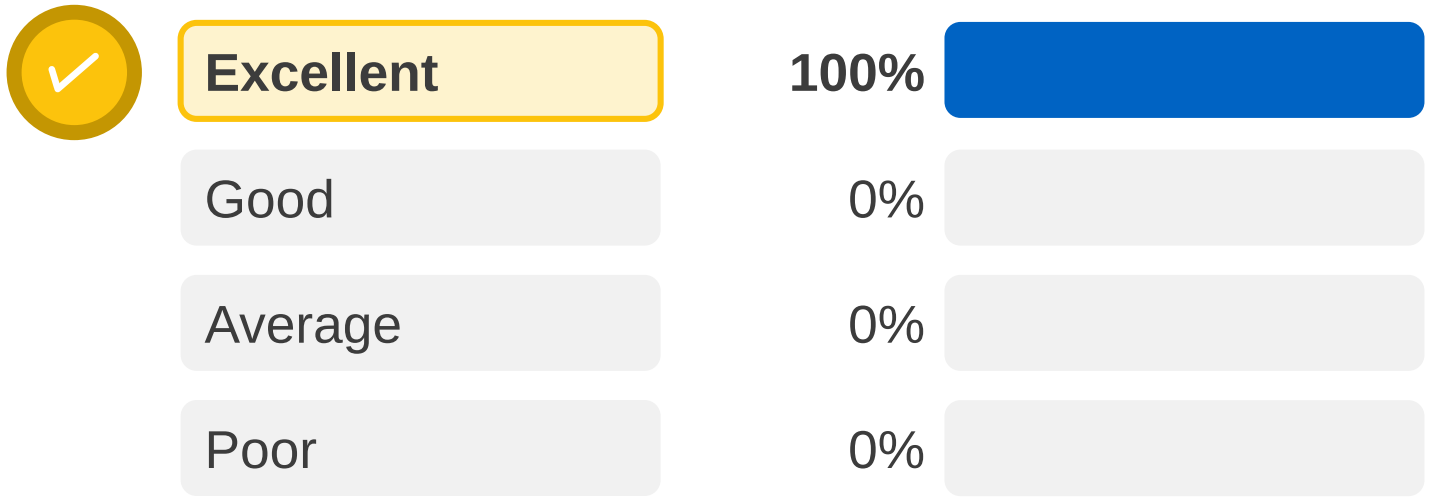
Excellent

Good

Average

Poor

How would you rate your current knowledge of the adverse event reporting process in clinical trials vs the real-world setting?



Introduction to Pharmacovigilance

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Which of the following statements best describes the activities covered by “drug safety (i.e., pharmacovigilance)”?

Detection and collection of adverse events

Evaluation and monitoring of adverse events

Understanding and preventing adverse events

All of the above

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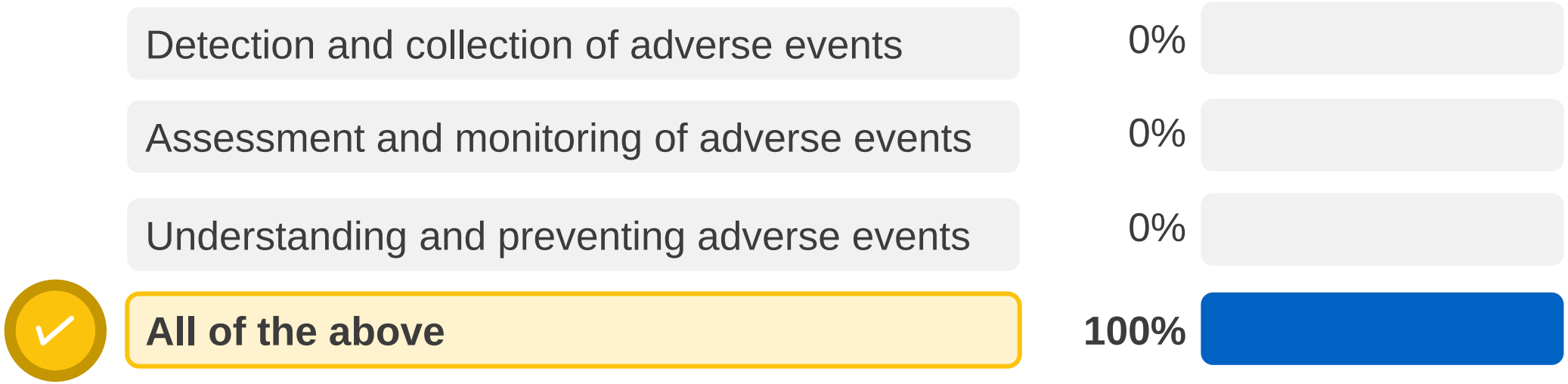
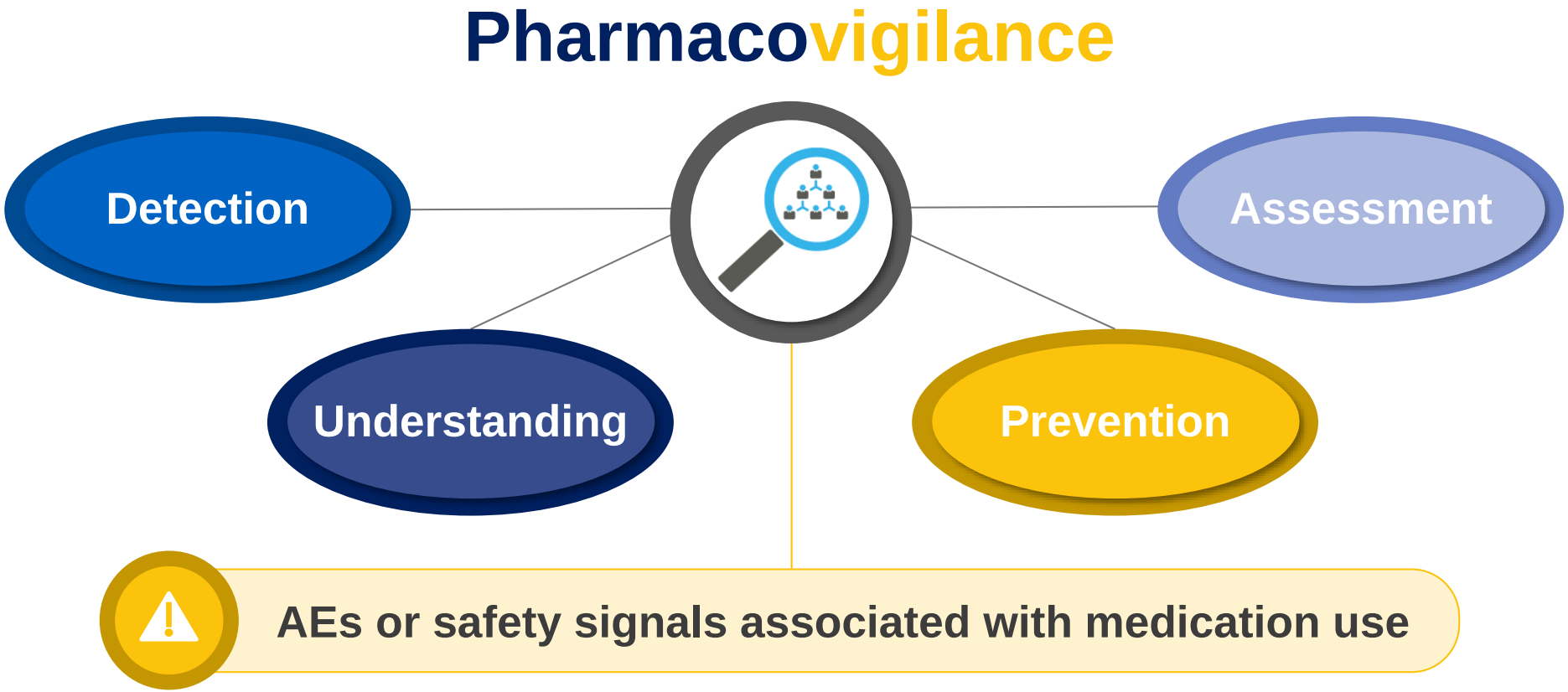
Which of the following statements best describes the activities covered by “drug safety (i.e., pharmacovigilance)”?



What is Pharmacovigilance?



Pharmacovigilance, also known as drug safety, is an umbrella term for all activities related to the detection, assessment, understanding and prevention of AEs or potential safety signals associated with medication use

Beninger P. *Clin Ther*. 2018;40(12):1991-2004.

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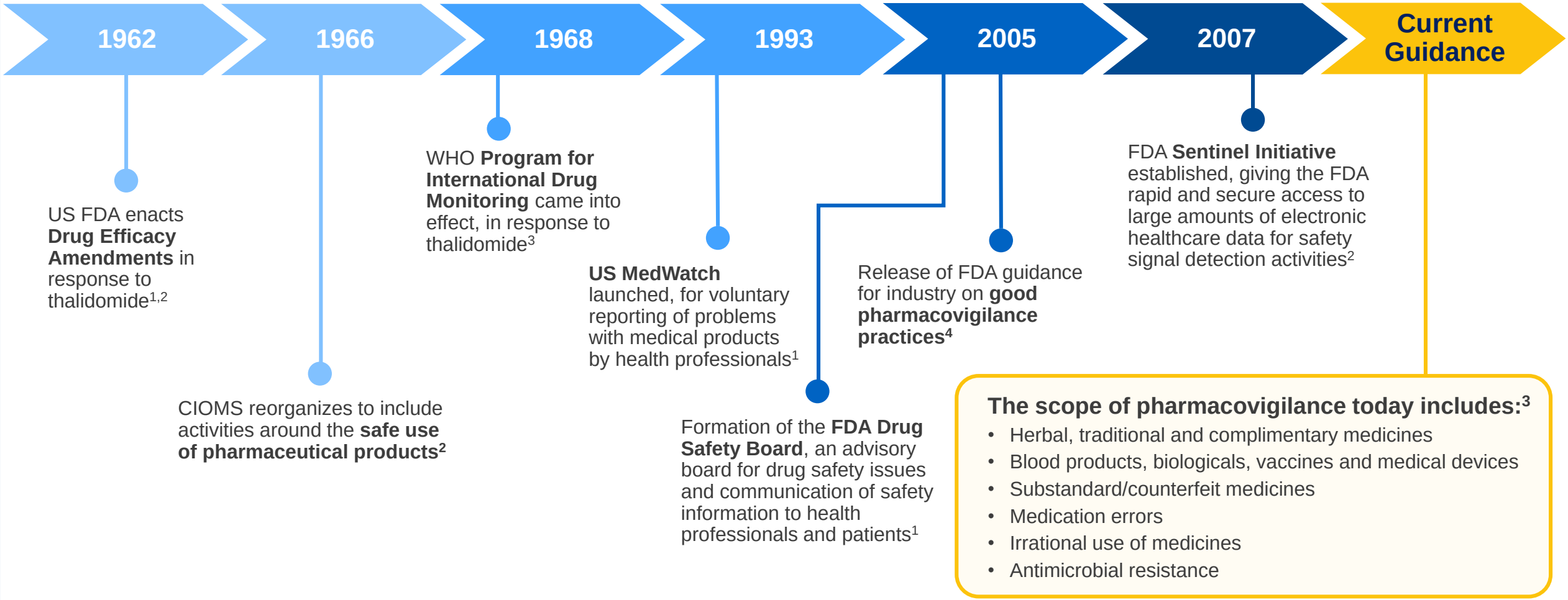
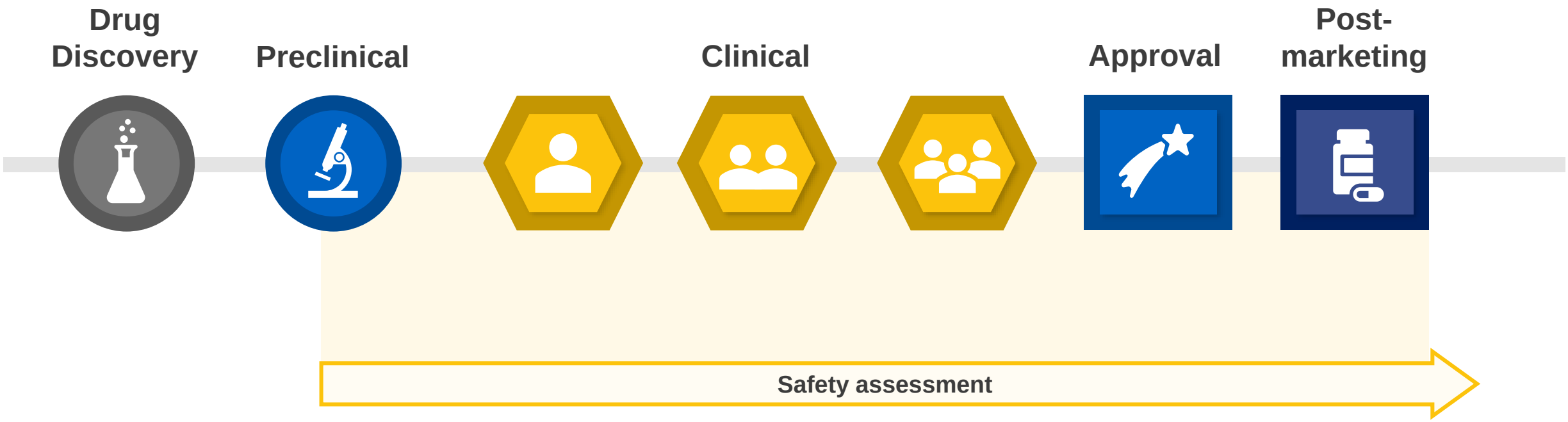
As a discipline, pharmacovigilance has grown rapidly over the past 20 years...[1,2]



CIOMS, Council for International Organizations of Medical Sciences.

1. FDA. (2018). Milestones in U.S. Food and Drug Law History. Available from: https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history. Accessed 28 February 2020; **2.** Beninger P. *Clin Ther*. 2018;40(12):1991-2004; **3.** WHO. Fast facts on Pharmacovigilance. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_fast_facts/en/. Accessed 28 February 2020; **4.** FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005.

...and now plays an important role throughout the drug life cycle[1-3]



In practice, understanding of a drug's safety profile begins during preclinical animal studies and is maintained throughout the drug's lifecycle for continuous collection of adverse events and evaluation of long-term safety[2]

1. FDA. (2016). Drug Safety Priorities: Initiatives and Innovation. Available from: https://www.fda.gov/media/100679/download. Accessed 28 February 2020.
2. Beninger P. *Clin Ther*. 2018;40(12):1991-2004. **3.** Dal Pan GJ. *Neurol Clin Pract*. 2015;5(4):338-43.

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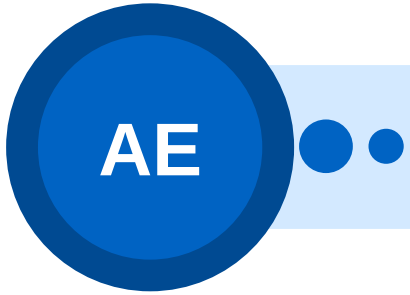
Assessment and monitoring of adverse events begins during clinical development and continues following approval[1]

At the time of drug approval, AE risks may not be fully defined.[2]
Therefore, the FDA maintains a system of post marketing surveillance to identify AEs that did not appear during clinical development and the drug approval process[3]



An adverse event is **any undesirable experience** associated with the use of a medical product in a patient[4]

The event is **serious** when the patient outcome is:[4]

- Death
- Life-threatening
- Hospitalization
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Important medical events*

*Event does not fit the other outcomes, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes (eg, seizures/convulsions that do not result in hospitalization).[4]

1. Beninger P. *Clin Ther*. 2018;40(12):1991-2004. **2.** Klein E, Bourdette D. *Neurol Clin Pract*. 2013;3(4):288-94. **3.** FDA (2016). Postmarketing Surveillance Programs. Available from: https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs. Accessed 28 February 2020. **4.** FDA. (2016). What is a Serious Adverse Event? Available from: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event. Accessed 28 February 2020.

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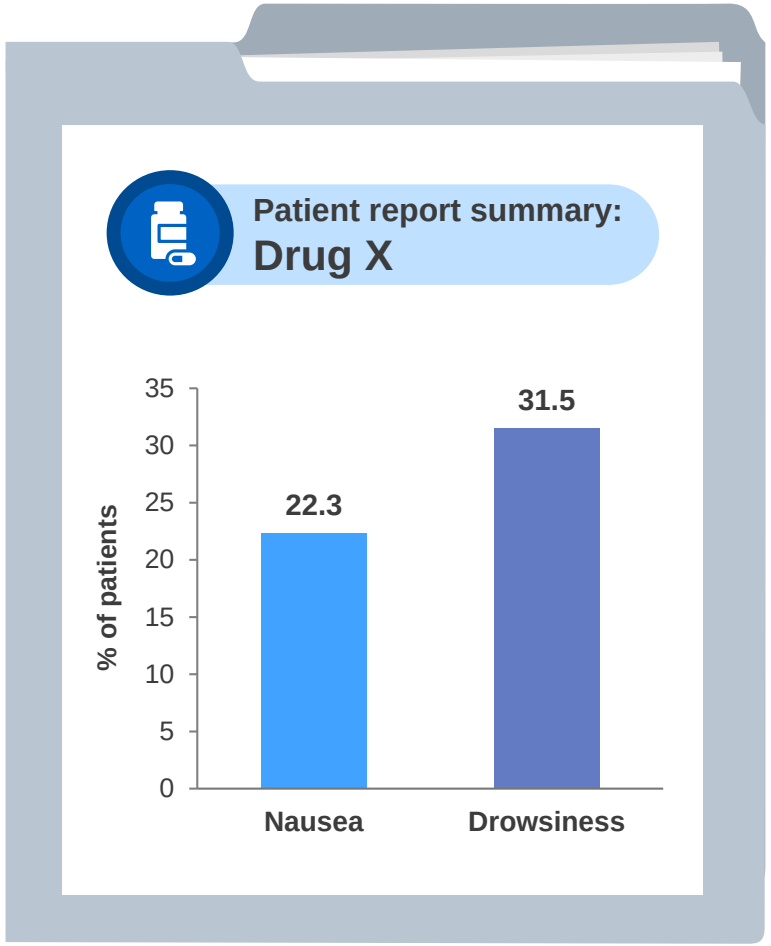
Case Study: Dr Smith

- Dr Smith is a general practitioner at Midtown Memorial Hospital
- Some of her patients are treated with Drug X, which was approved by the FDA 6 months ago
- Recently, she has noticed that some of these patients report experiencing nausea and drowsiness
- She consults the other physicians in her department and compiles available data for patients treated with Drug X
- The data she collects show nausea and drowsiness were reported by 22.3% and 31.5% of patients treated with Drug X, respectively
- No reported cases resulted in hospitalization or death



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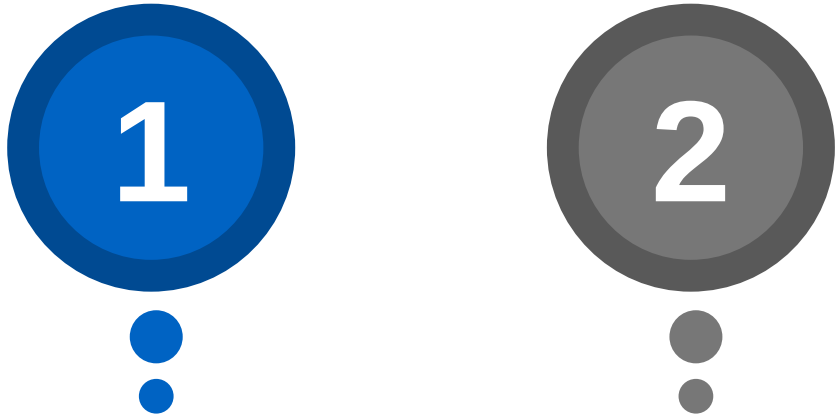
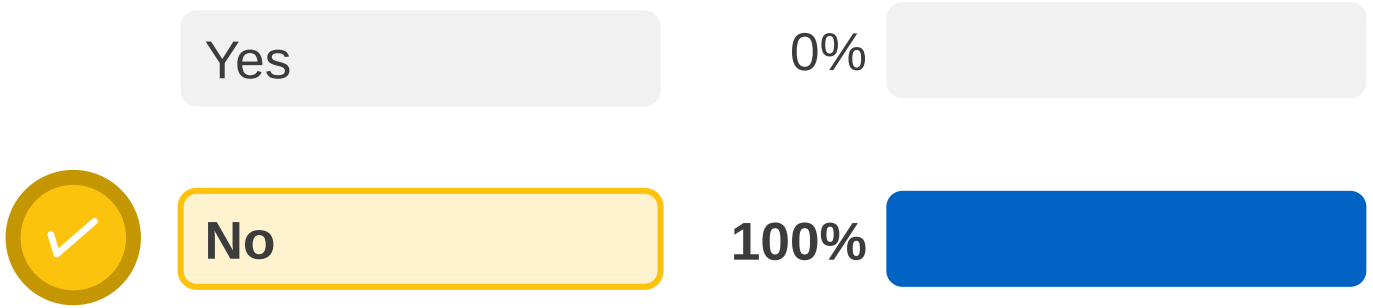
Do the symptoms experienced by Dr Smith's patients fall under the category of serious adverse events?



Yes

No

Do the symptoms experienced by Dr Smith’s patients fall under the category of serious adverse events?



Considerations for AE Reporting in Clinical Trials vs Real World

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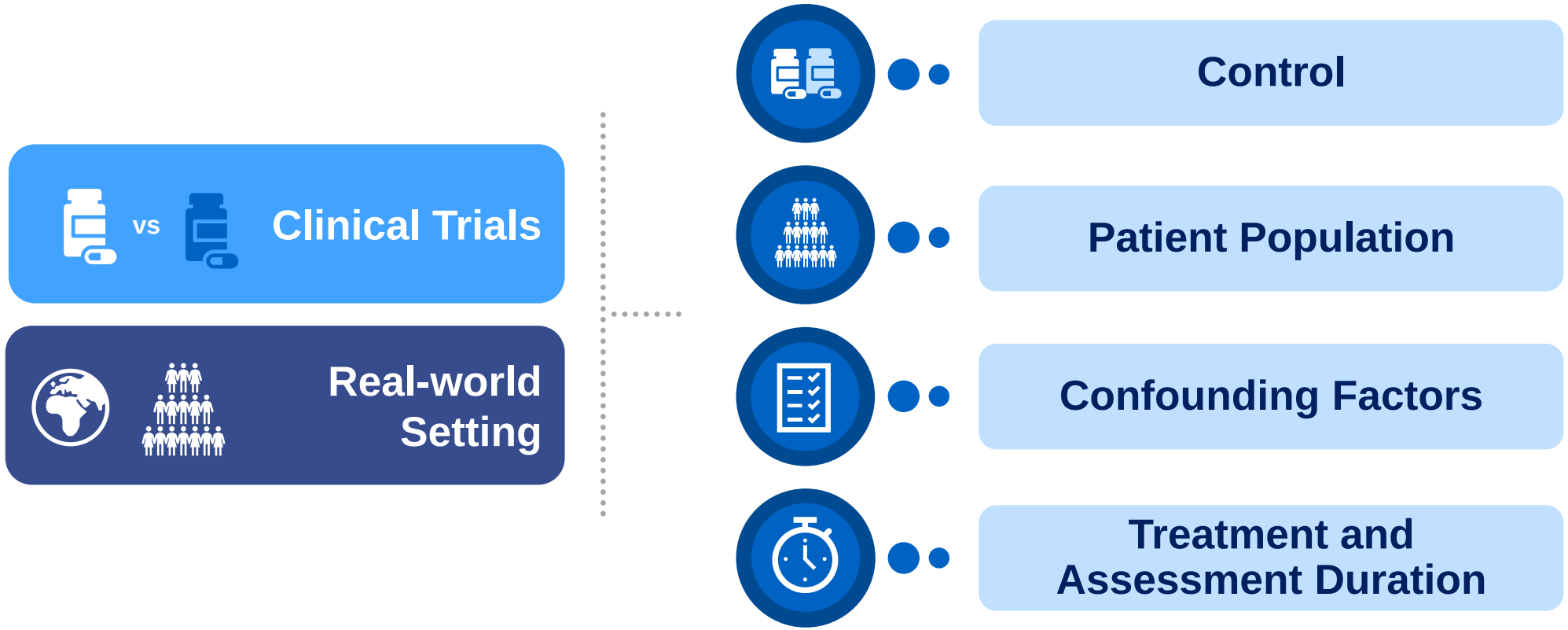
Overview: Considerations for Reporting AEs in Clinical Trials vs the Real-World Setting



The different considerations for AEs reported in clinical trials versus the real-world setting will be discussed in more detail throughout this talk

WHO. Open Access to the WHO Global Pharmacovigilance Data base. Available from: www.who.int/medicines/news/glob_pharmvig_database_qa/en/. Accessed 28 February 2020.

Unlike the real-world setting, the impact of a treatment in clinical trials may be compared with the outcome of the control group[1-4]

Control

Controlled trials[1-4]

- Incidence of AEs in patients receiving the drug of interest is compared with the AEs occurring in a **control population**[1-3]
  - eg, patients receiving placebo
- Comparison of a test treatment against a control allows **evaluation of outcomes that may be caused by other factors** such as natural disease progression[4]

Real-world setting[5-7]

- **No control** or active comparator
- Without a control group, **outcomes in real-world settings are not contextualized,** making it difficult to quantify risk

1. Berlin JA, et al. *Am J Public Health*. 2008;98(8):1366-1371; **2.** Ioannidis JPA, et al. *Ann Intern Med*. 2004;141(10):781-788; **3.** Lineberry N, et al. *BMJ*. 2016;355:i5078.
4. FDA. Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. 2001. **5.** Blonde L, et al. *Adv Ther*. 2018:35:1763–1774. **6.** Singh S, Loke YK. *Trials*. 2012;13:138.
7. Camm AJ, Fox KAA. *Open Heart* 2018;5:e000788.

Patient populations in the clinical trial setting can differ from those in the real world[1-5]

Patient Population

Clinical trials[1-3]

- **Study populations are smaller** and may be selected based on statistical considerations
- Participants selected based on restricted, **pre-specified eligibility criteria**

Real-world setting[4,5]

- Treated population is larger and more **heterogeneous**
- Treated population may have more **comorbidities and/or other confounding factors**
- Patients may be receiving additional **concomitant medications**

1. Berlin JA, et al. *Am J Public Health*. 2008:98:1366–1371. **2.** Singh S, Loke YK. *Trials*. 2012;13:138; **3.** WHO. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. 2002; **4.** FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; **5.** Kumar A. *Am J Health-Syst Pharm*. 2017;74(8):606-612.

Confounding factors in the real world can make determination of causality a challenge[1,2]

Confounding factors in **RCTs** are reasonably well-identified[1]

In the **real-world setting,** unaccounted for, or unidentified **confounding factors** can make it challenging to establish a causal relationship between a drug and an AE[1]

- Spontaneously reported data to the drug manufacturer may be incomplete or confounded by the co-existence of **other medical conditions or medications** that could either be the cause of, or a contributing factor to, the event in question[1,2]
- The incidence of real-world AEs includes **background rates** of the affected population in the absence of the treatment of interest[1]

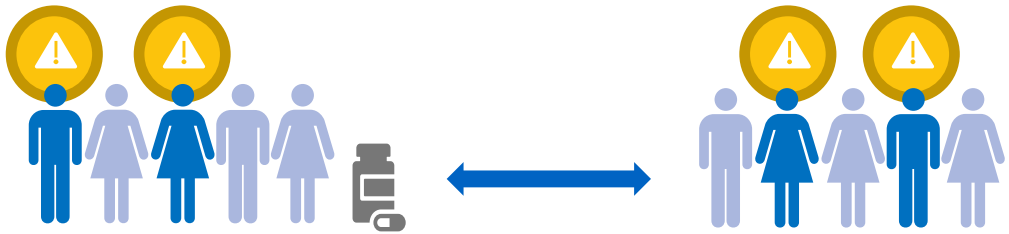
AE, adverse event; **RCT,** randomized controlled trials.

1. FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; **2.** EMA. Guideline on good pharmacovigilance practices (GVP). 2017.

How do background rates contextualize reported data?

The **occurrence of a reported AE** needs to be put into context

- The occurrence of a reported AE is compared to an estimate of the **background rate** of occurrence for that AE in the **general population**
- Ideally, the **rate of occurrence** for the event in a subpopulation is similar to that of the population exposed to the drug eg, patients with diabetes, post-menopausal women



Sources of background rates include:

- National health statistics
- Published literature
- Studies using large databases
- Ongoing epidemiological investigations

FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005.

Treatment and assessment duration differ between clinical trials and the real world[1]

Clinical trials[1-7]

- Participants receive the study drug for a **relatively short period of time** and are **monitored continuously** (per study protocol)[1,2]
- AEs are collected and assessed throughout the **study duration** for all phases[1,3-7]

DBTP, double-blind treatment period; **OLTP,** open-label treatment phase.

1. Berlin JA, et al. *Am J Public Health*. 2008;98(8):1366-1371; **2.** Kim H-S, et al. *J Korean Med Sci*. 2018;33(34):e213. **3.** FDA. Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006; **4.** FDA. Guidance for Industry. Safety Labeling Changes. 2013; **5.** Lineberry N, et al. *BMJ*. 2016;355:i5078; **6.** Singh S, Loke YK. *Trials*. 2012;13:138; **7.** WHO. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. 2002.

Treatment and assessment duration differ between clinical trials and the real world[1]

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AE assessments in clinical trials may be:[8]

- **Unprompted** (spontaneous) – open-ended questions about **any AEs**, as part of a diary or questionnaire
- **Prompted** – elicited based on a **list of possible AEs**

Factors that may influence AE reporting in clinical trials include the collection method used, informed consent wording, and language translation[8,9]

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Treatment and assessment duration differ between clinical trials and the real world[1]

Treatment and Assessment Duration

Clinical trials[1-7]

- Participants receive the study drug for a **relatively short period of time** and are **monitored continuously** (per study protocol)[1,2]
- AEs are collected and assessed throughout the **study duration** for all phases[1,3-7]

DBTP → **OLTP**

~ Weeks to months[4-7] → ~ Months to years[4-7] →

Real-world setting

- In the real-world setting patients may take the drug for a **longer duration** and receive **variable monitoring**[1,2]
- AEs are collected and assessed from the time of approval **throughout the drug's lifecycle**[8,9]

Post-marketing phase

Indefinite monitoring[8,9] →

DBTP, double-blind treatment period; **OLTP,** open-label treatment phase.

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Different considerations exist between AEs that are reported in clinical trials and in the real-world setting

	Clinical Trials	Real-world Setting
Control	Placebo- or active-control[1-3]	No placebo- or active-control[1-3]
Patient Population	Smaller patient population selected according to pre-specified eligibility criteria[4,5]	Larger and more heterogeneous patient population (eg, more complex comorbidities)[6,7]
Confounding Factors	Confounding factors well defined[7]	Confounding factors may be unidentified or misunderstood[7,*]
Treatment and Assessment Duration	Patients are treated and AEs are assessed for defined periods of time (~ months)[2,4,5]	Patients may be treated, and AEs monitored, indefinitely[8,9]

Drug manufacturers must report all AEs to regulatory agencies
regardless of causality in accordance with reporting timeline requirements[3,8-11]

*eg, the incidence of real-world AEs includes background rates of the patient population.

1. Ioannidis JPA, et al. *Ann Intern Med*. 2004;141(10):781-788; **2.** Lineberry N, et al. *BMJ*. 2016;355:i5078; **3.** Berlin JA, et al. *Am J Public Health*. 2008;98(8):1366-1371; **4.** Singh S, Loke YK. *Trials*. 2012;13:138; **5.** WHO. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. 2002; **6.** Kumar A. *Am J Health-Syst Pharm.* 2017;74(8):606-612; **7.** FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; **8.** FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers. Accessed 28 February 2020; **9.** FDA. Guidance for Industry. Providing Submissions in Electronic Format-Postmarketing Safety Reports. 2014; **10.** FDA. Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006; **11.** FDA. Guidance for Industry. Safety Labeling Changes. 2013.

Dr Smith is not sure that the nausea and drowsiness her patients have reported are caused by Drug X. Which of the following factors make it challenging to determine causality between Drug X and these AEs?

AE rates for Drug X are not compared against a control group (eg, placebo)

Data collected regarding the AEs reported by patients taking Drug X may be incomplete

The patient population receiving Drug X is likely to be heterogenous and so there may be unidentified or unaccounted for confounding factors

All of the above

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Which of the following factors make it challenging to determine causality between Drug X and these AEs?

AE rates for Drug X are not compared against a control group (eg, placebo)	0%
Data collected regarding the AEs reported by patients taking Drug X may be incomplete	0%
The patient population receiving Drug X is likely to be heterogenous and so there may be unidentified or unaccounted for confounding factors	0%
✓ **All of the above**	**100%**

Detection, Evaluation, and Management of Safety Signals

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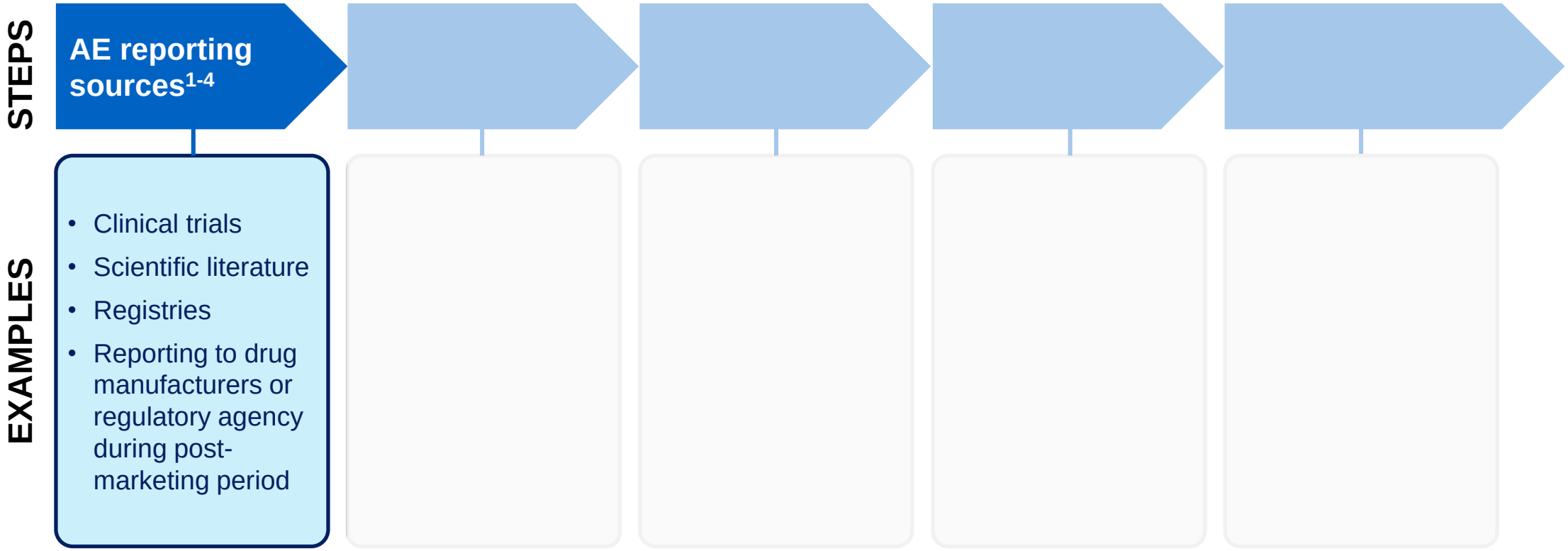
A number of steps facilitate the timely detection, evaluation, and management of safety signals



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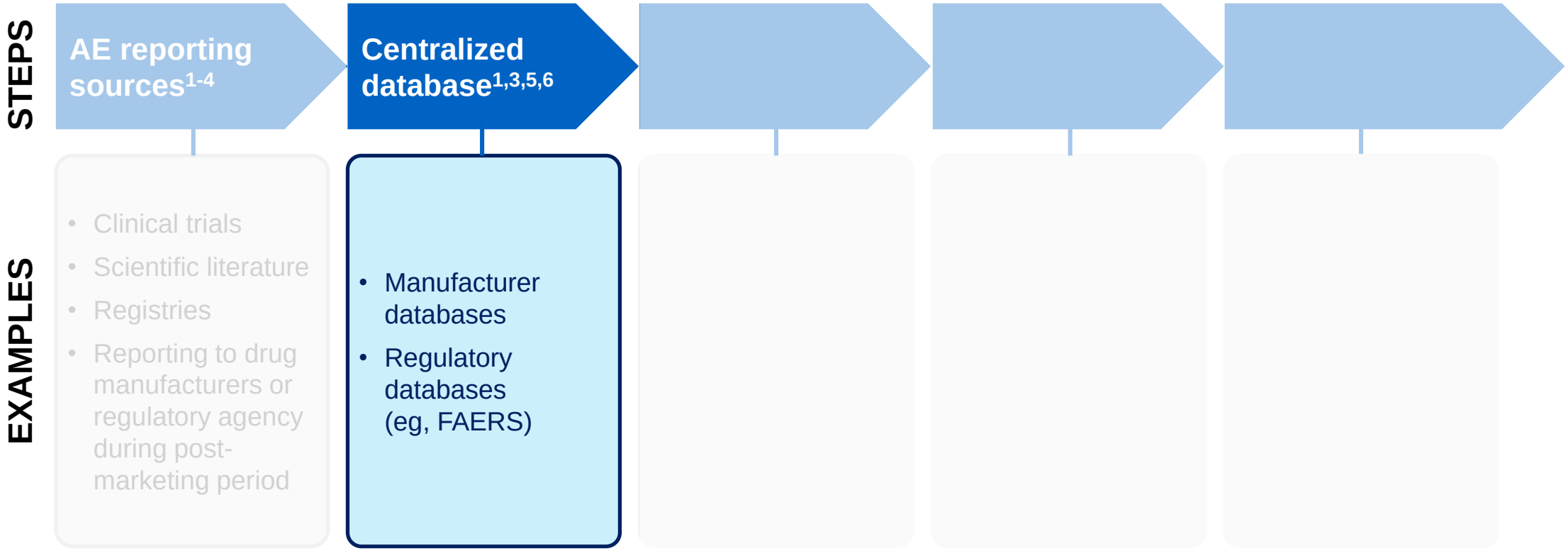

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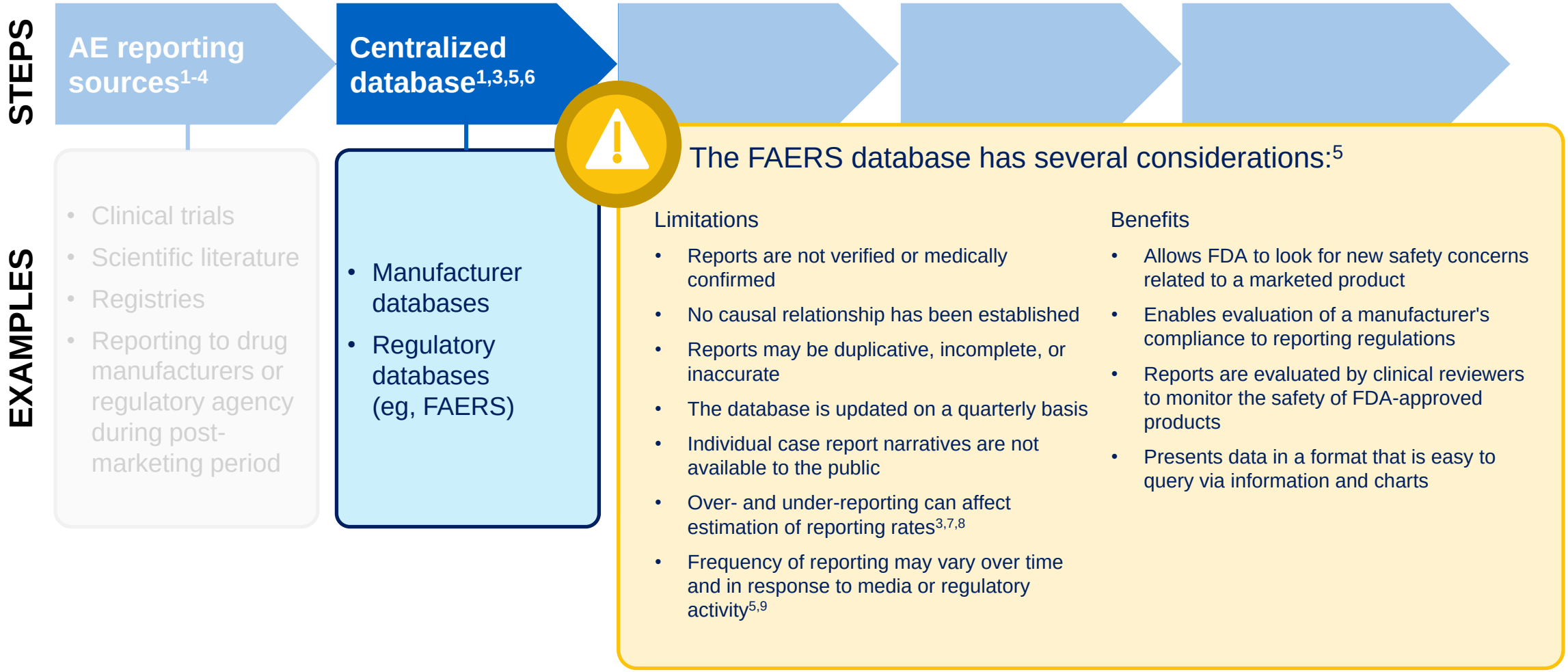

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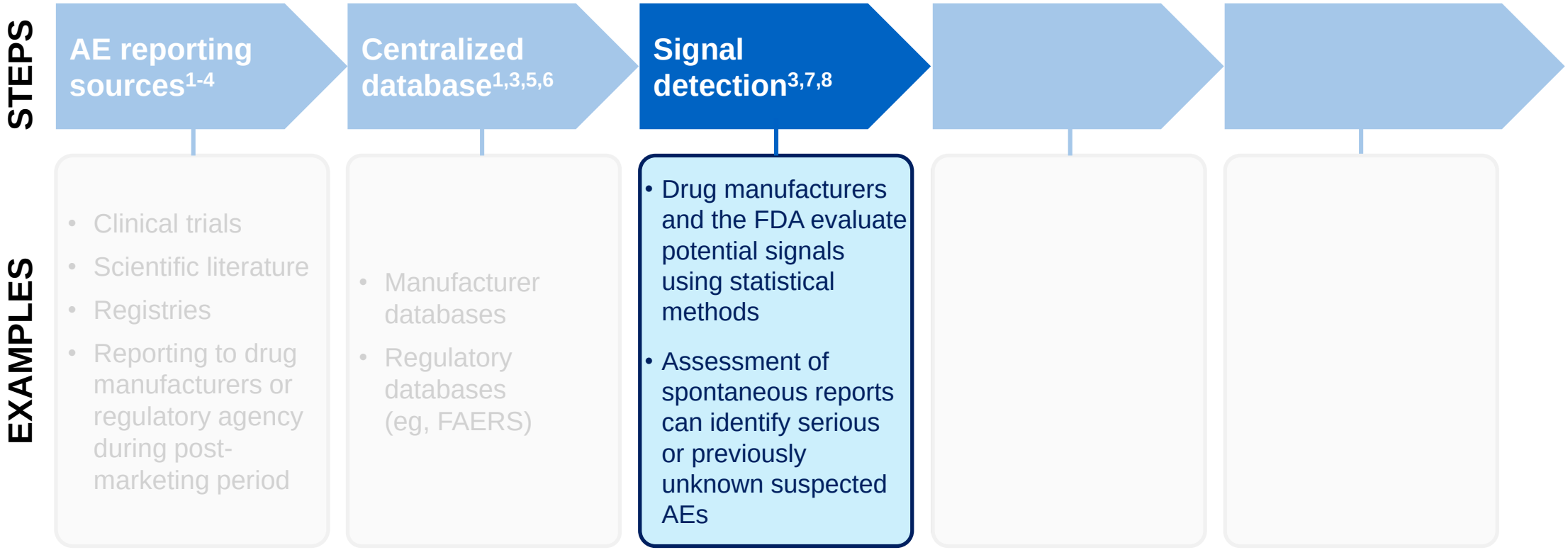

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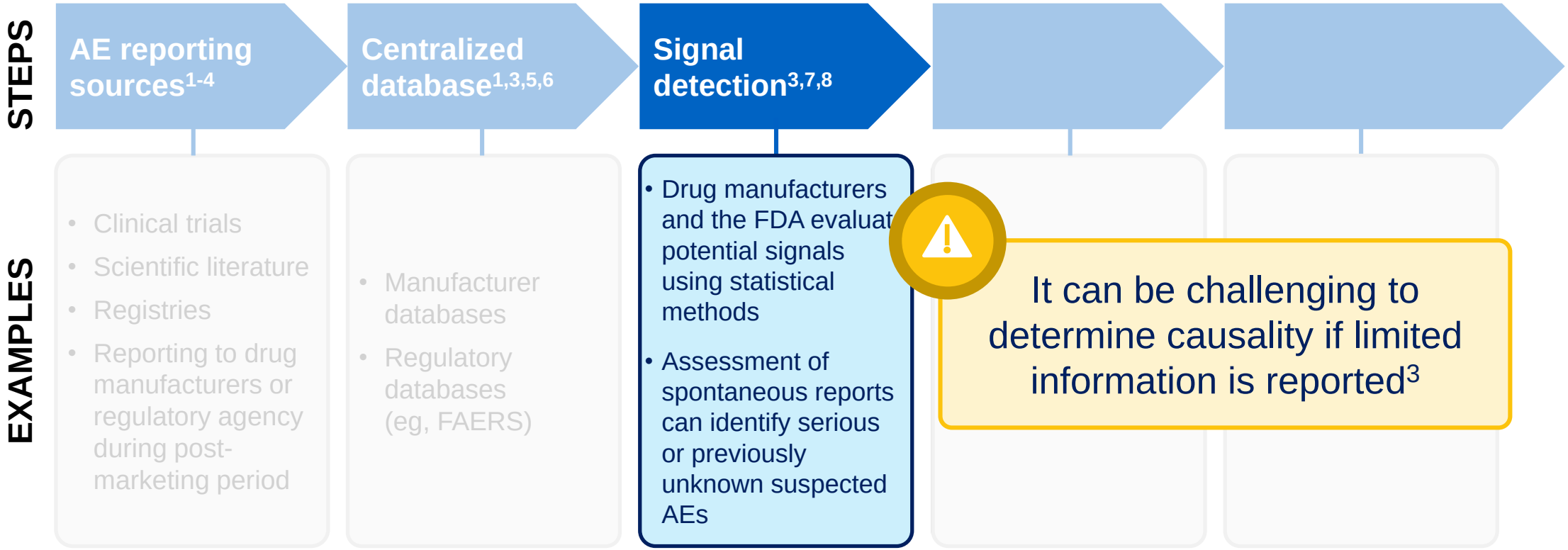
A number of steps facilitate the timely detection, evaluation, and management of safety signals



1. Beninger P. *Clin Ther*. 2018;40(12):1991-2004; **2.** FDA. Guidance for Industry. Safety Labeling Changes. 2013; **3.** FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005; **4.** EMA. Guideline on good pharmacovigilance practices (GVP). 2017; **5.** FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). Available from: www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers. Accessed 28 February 2020; **6.** WHO. Open Access to the WHO Global Pharmacovigilance Data base. Available from: www.who.int/medicines/news/glob_pharmvig_database_qa/en/. Accessed 28 February 2020; **7.** Koutkias VG, Jaulent MC. *Drug Saf*. 2015;38(3):219-232; **8.** EMA. Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines. 2017.

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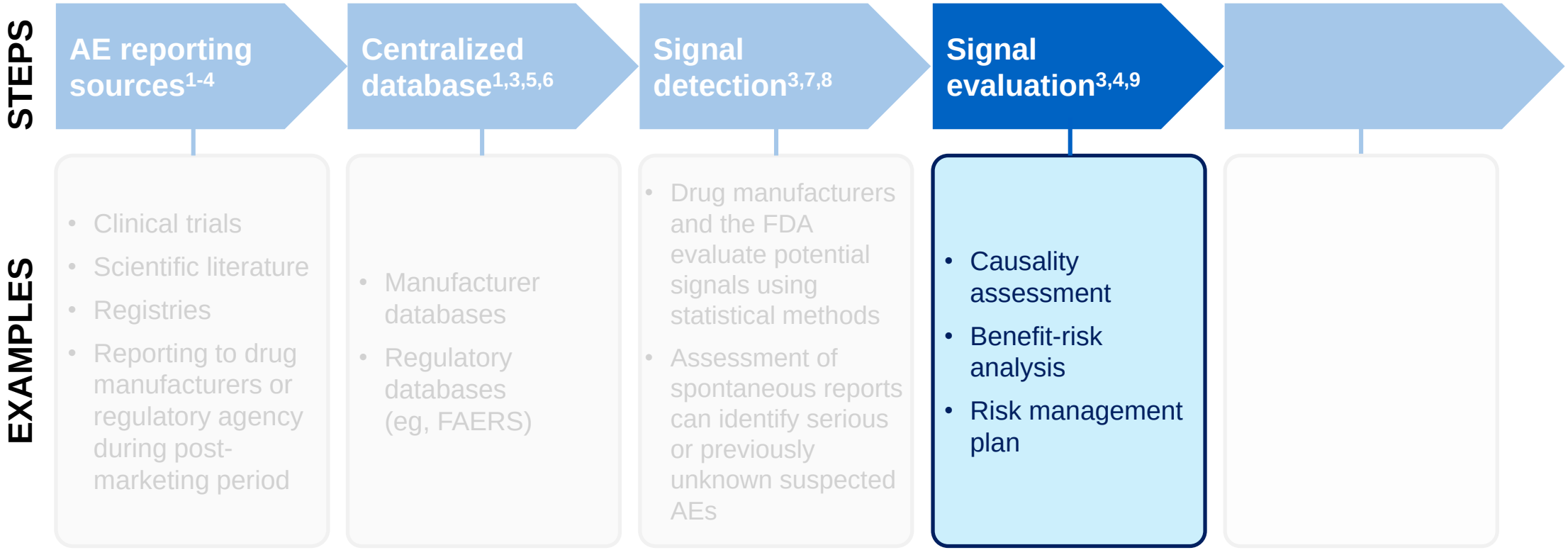

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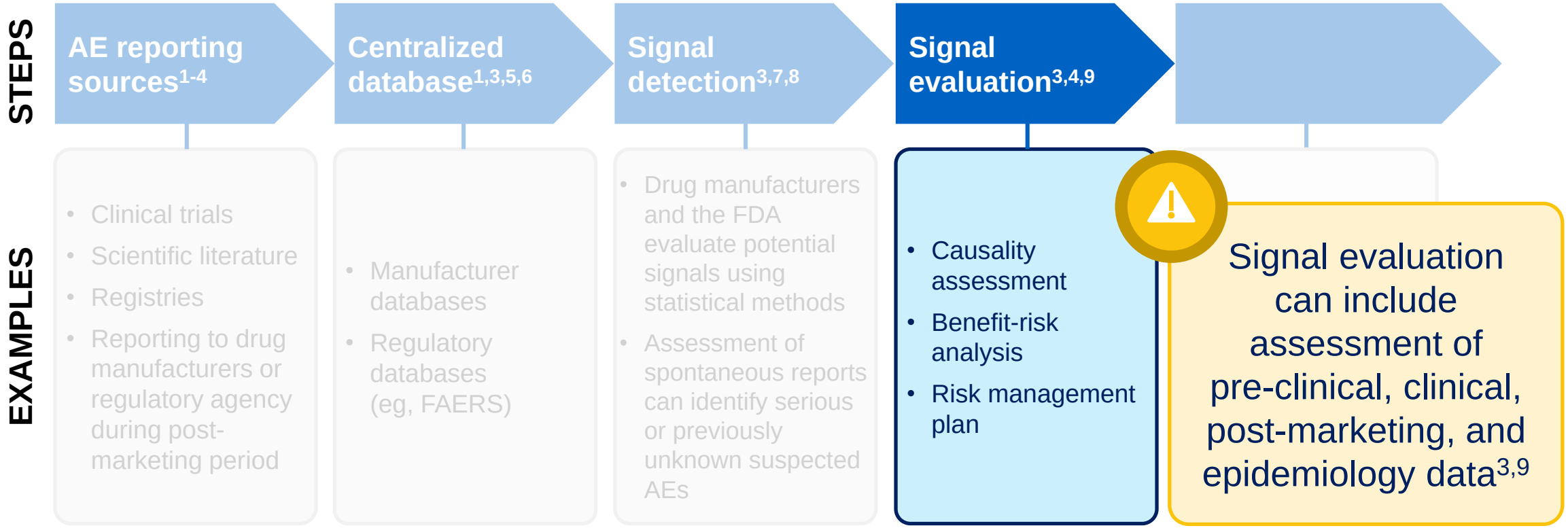

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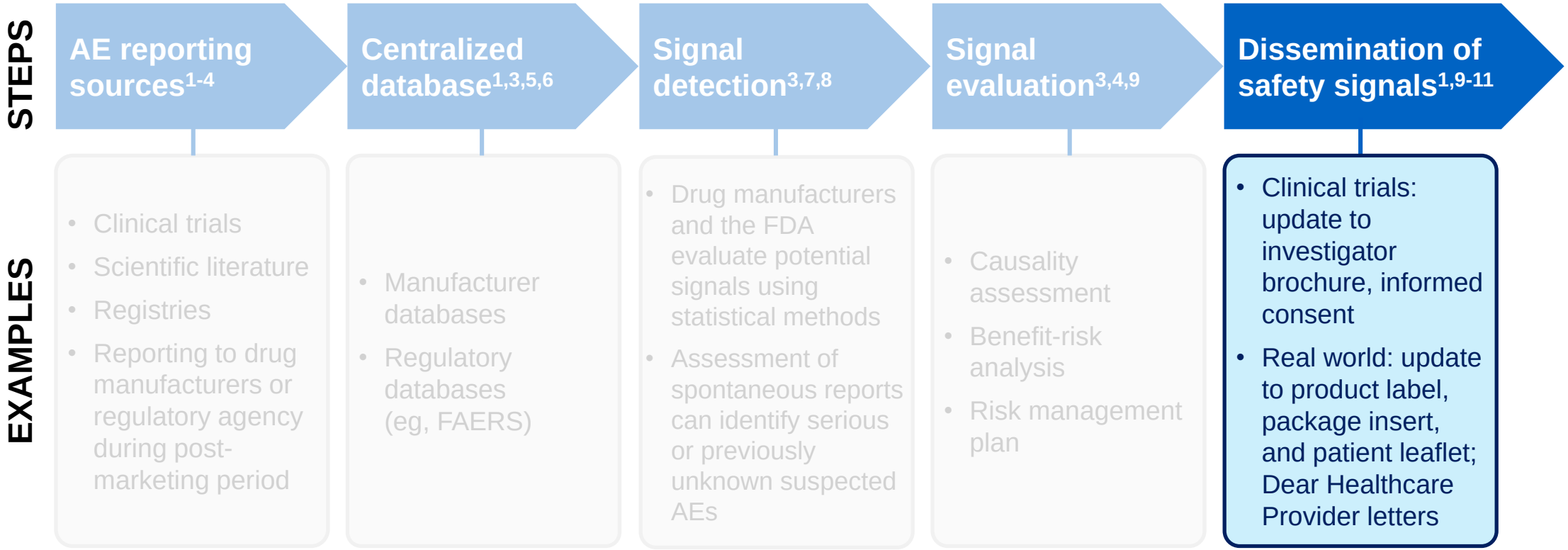

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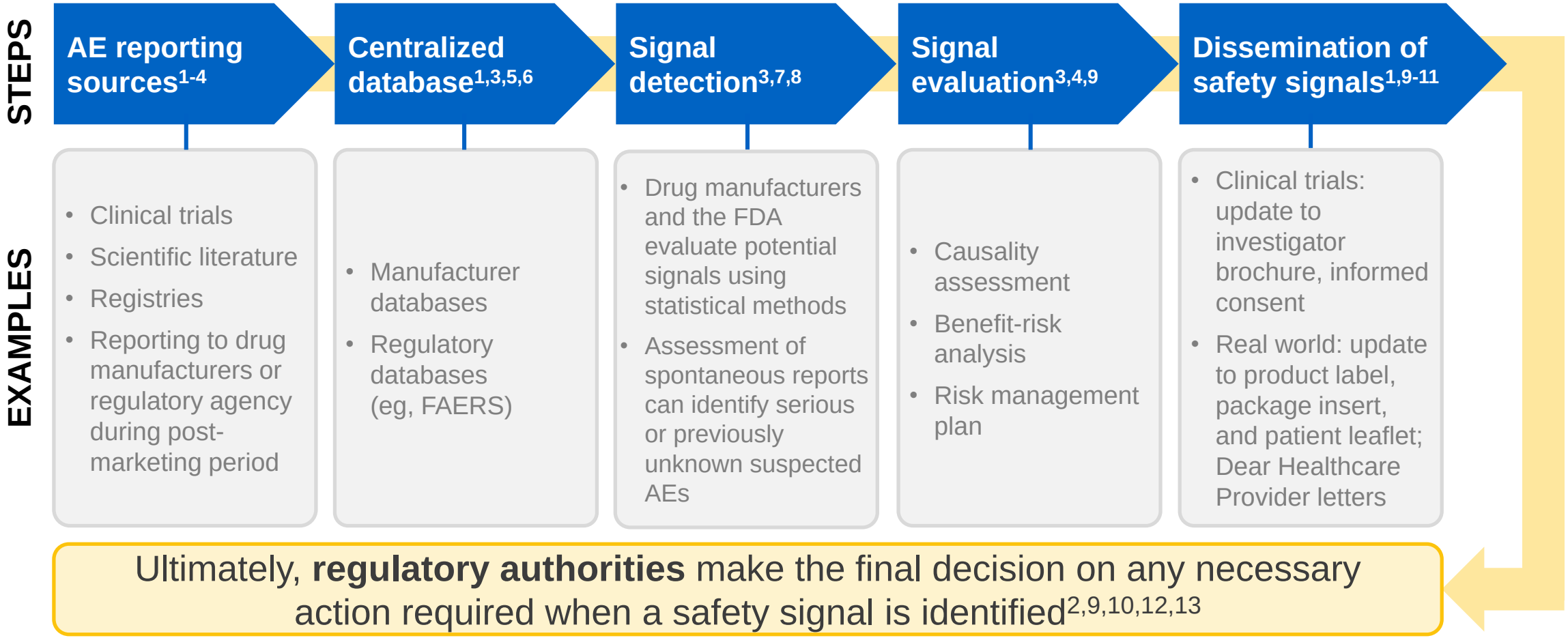

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Role of Healthcare Professionals

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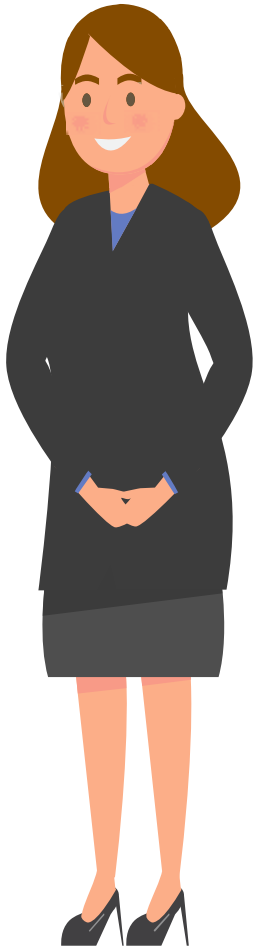
Pharmacovigilance in the real-world setting – your role as an HCP

Healthcare providers are at the forefront of pharmacovigilance because they are involved in:[1]

- **Prescribing the drug**
- **Managing any AEs**



As such, HCPs are well equipped to report AEs regardless of causality

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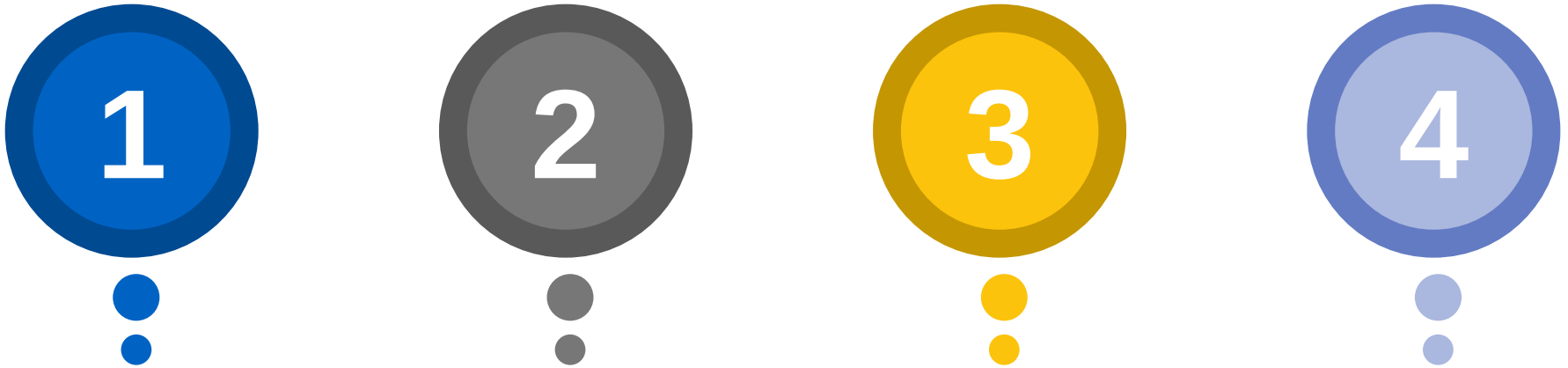
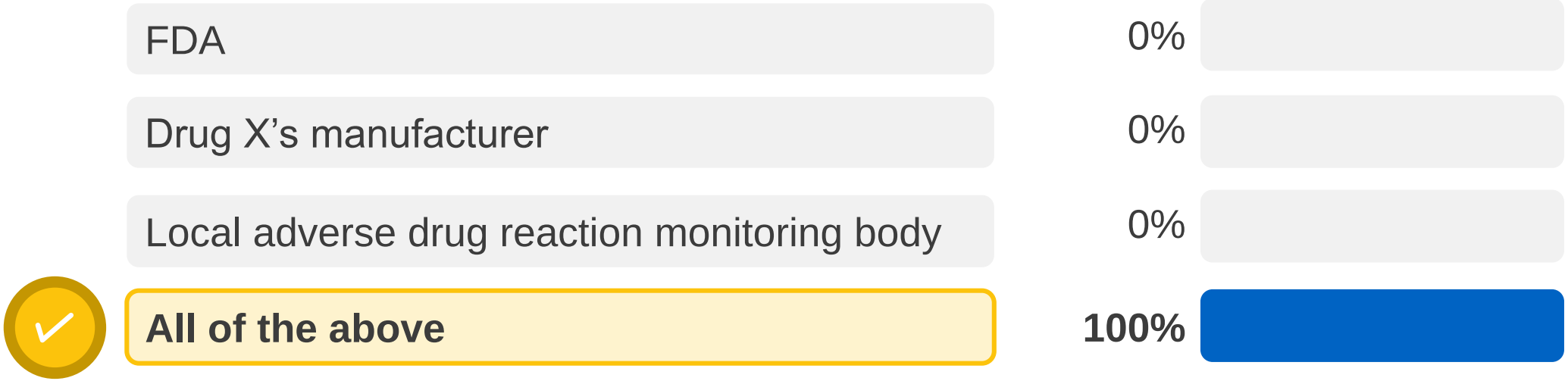
1. Klein E, Bourdette D. *Neurol Clin Pract*. 2013;3(4):288-94.

Dr Smith suspects there may be a causal relationship between Drug X and the observed AEs. She thinks it is important to report her findings but she is unsure of who to contact. Dr Smith can report these AEs to which of the following?



1. FDA
2. Drug X's manufacturer
3. Local adverse drug reaction monitoring body
4. All of the above

Dr Smith can report these AEs to which of the following?



There are a number of ways healthcare providers can report AEs[1,2]

FDA

Directly to the **FDA** through the Medwatch program, either by phone, online, or by post

Directly to the **drug manufacturer**

By contacting **the local adverse drug reaction monitoring body**, eg, institutional committee responsible for monitoring AEs

1. Klein E, Bourdette D. *Neurol Clin Pract*. 2013;3(4):288-94; **2.** Dal Pan GJ. *Neurol Clin Pract*. 2015;5(4):338-43.

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What Information is Required to Make a Report Valid and Complete?

≥ 1 identifiable reporter[1]

- Profession* (eg, physician, pharmacist)[2]
- Name or address[2]
- Contact details for follow-up, if possible[2]

1 identifiable patient[1]

- Information allowing the existence of the patient to be verified[2], eg:
  - Initials[2]
  - Medical record number[2]
  - Date of birth, age, age group, gender[2]

≥ 1 suspected drug or medicinal product[1]

≥ 1 adverse event[1]

*Reporter is not required to be a healthcare professional to be considered a valid reporter.[3]

1. FDA. Guidance for Industry. Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report. 1997.
2. EMA. Guideline on good pharmacovigilance practices (GVP). 2017. **3.** FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers. Accessed 28 February 2020.

What Information Makes a Good Report?

Patient characteristics

- Demographics, baseline medical condition, comorbid conditions, concomitant medications, family history, risk factors

Additional details

- Laboratory data at baseline, during and after therapy
- Response to dechallenge and rechallenge
- Any other relevant information (eg, other details related to the event)

AE description

- Time to onset of signs and symptoms
- AE diagnosis and diagnostic methods
- AE clinical course and patient outcomes (eg, hospitalization or death)

Suspected & concomitant therapies

- Dose, lot number, schedule, dates, duration. Includes over the counter medication, dietary supplements, and recently discontinued medications

FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005.

What happens after a HCP reports AE to the drug manufacturer?

Once an AE is reported to the drug manufacturer:

AEs are communicated to the FDA according to prespecified timelines, regardless of causality[1]

For example, serious, unexpected post market adverse events are required to be reported to the FDA within 15 calendar days[2]

After submitting a report, there may be continued communication between the FDA, the drug manufacturer, and/or the HCP reporter to obtain additional details[3]

Submitted reports are processed and uploaded into the FAERS database, where they are made publicly available[4]

By accessing the FAERS public dashboard, the public can view summaries of adverse event reports[1]

1. FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers. Accessed 28 February 2020.
2. FDA. Guidance for Industry. Providing Regulatory Submissions in Electronic Format-Receipt Dates. 2014. **3.** FDA. Guidance for Industry. Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report. 1997. **4.** FDA. Guidance for Industry. Providing Submissions in Electronic Format-Postmarketing Safety Reports. 2014.

After some research Dr Smith decides to report the AEs to Drug X's manufacturer. However, she begins to question this decision after a co-worker tells her that drug manufacturers only evaluate and report serious AEs to the FDA. Is this true?

No

All AEs reported to a drug manufacturer **must be reported to the FDA, regardless of causality**

No

AEs reported to a drug manufacturer **only need to be reported to the FDA if there is a suspected causal relationship** between the drug and the AE

Yes

AEs reported to a drug manufacturer **only need to be reported to the FDA if they are serious in nature or are not already included in the product's label**

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Is this true?

No – all AEs reported to a drug manufacturer must be reported to the FDA, regardless of causality	**100%**
No – AEs reported to a drug manufacturer only need to be reported to the FDA if there is a suspected causal relationship between the drug and the AE	0%
Yes – AEs reported to a drug manufacturer only need to be reported to the FDA if they are serious in nature or are not already included in the product's label	0%

Summary

Pharmacovigilance, or drug safety, plays an integral role in the drug life cycle[1-3]

Assessment and monitoring of drug safety begins before approval and continues for as long as the drug is available on the market[2]

Limitations of data from spontaneous reporting can make it challenging to determine causality in the real-world setting without full safety evaluation incorporating other data from clinical, nonclinical, and epidemiology studies[4,5]

Although different factors should be considered when evaluating AEs reported in the real world and clinical trials, together they help reflect the product's safety profile[6]

There are defined processes for reporting, evaluating, and managing safety signals, and healthcare providers, caregivers, and patients play an important role in the reporting of AEs associated with medication use[7]

1. FDA. (2016). Drug Safety Priorities: Initiatives and Innovation. Available from: https://www.fda.gov/media/100679/download. Accessed 28 February 2020. 2. Beninger P. *Clin Ther*. 2018;40(12):1991-2004. 3. Dal Pan GJ. *Neurol Clin Pract*. 2015;5(4):338-43. 4. FDA. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005. 5. EMA. Guideline on good pharmacovigilance practices (GVP). 2017. 6. Klein E, Bourdette D. *Neurol Clin Pract*. 2013;3(4):288-94. 7. WHO. Open Access to the WHO Global Pharmacovigilance Data base. Available from: www.who.int/medicines/news/glob_pharmvig_database_qa/en/. Accessed 28 February 2020.

After this presentation, how would you rate your knowledge of the adverse event reporting process in clinical trials vs the real-world setting?

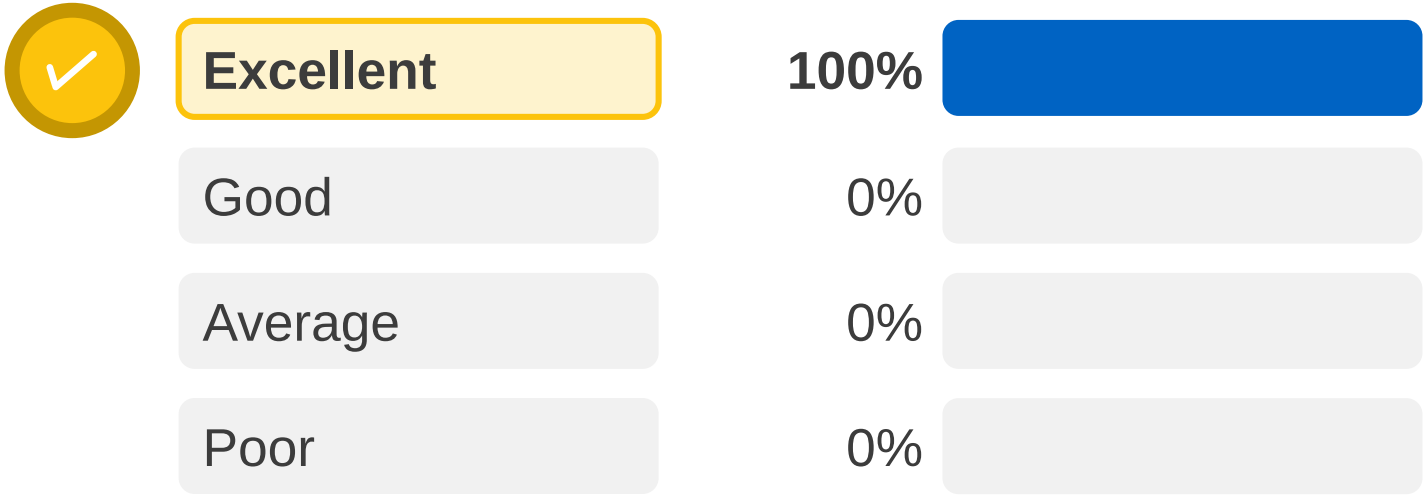
Excellent

Good

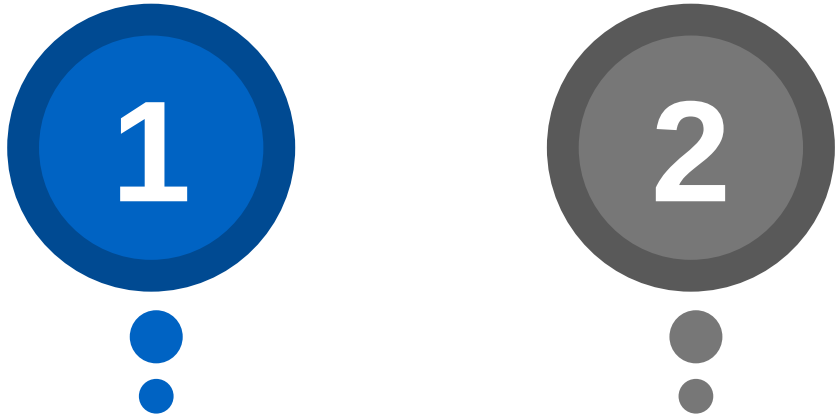
Average

Poor

After this presentation, how would you rate your knowledge of the adverse event reporting process in clinical trials vs the real-world setting?



Did you find the information presented here to be helpful in understanding post-marketing safety surveillance?



Yes

No

Did you find the information presented here to be helpful in understanding post-marketing safety surveillance?

Q&A

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Thank you

What challenges are involved in determining causality between a reported AE and a drug in the real world?

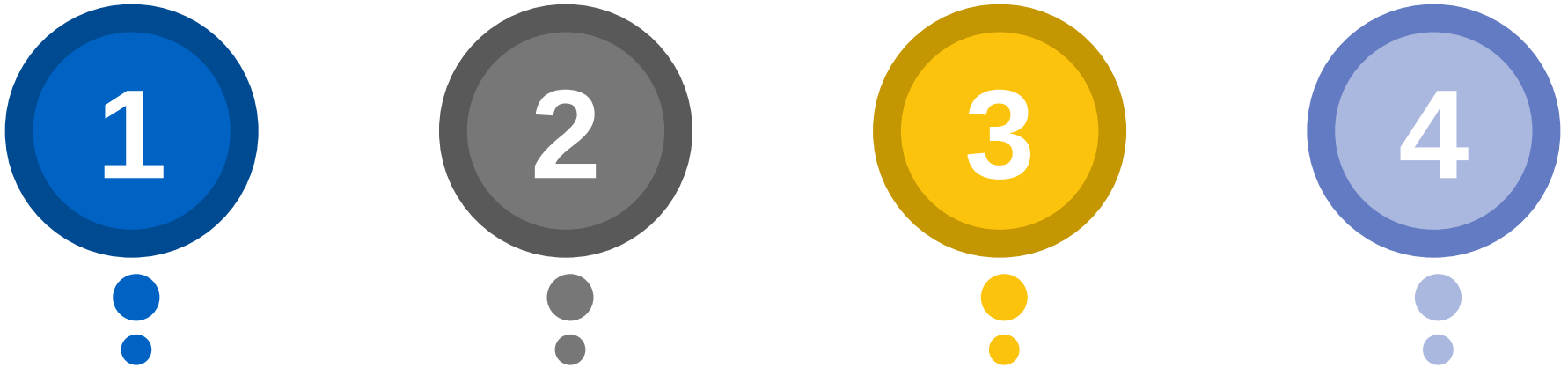
AE rates for a drug are not compared against a control group (eg, placebo) in the real-world setting

Data regarding AEs reported in the real world may be incomplete

There may be unidentified or unaccounted for confounding factors given the heterogeneity of the patient population

All of the above

Healthcare providers are able to report AEs to which of the following?



1. FDA
2. The drug manufacturer
3. Local adverse drug reaction monitoring body
4. All of the above

Which of the statements below is true?

All real-world AEs reported to a sponsor company **must be reported to the FDA, regardless of causality**

Real-world AEs reported to a sponsor company **only need to be reported to the FDA if there is a suspected causal relationship** between the drug and the AE

Real-world AEs reported to a sponsor company **only need to be reported to the FDA if they are serious in nature or are not already included in the product's label**

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Excellent

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Average

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