



# O papel da integração de sistemas de registos clínicos nas bases de dados de Farmacovigilância

Ana Azevedo, MD, PhD



30º Aniversário do SNF - Dia da Farmacovigilância  
13 Dez 2022





# **O papel da integração de sistemas de registos clínicos nas bases de dados de Farmacovigilância**

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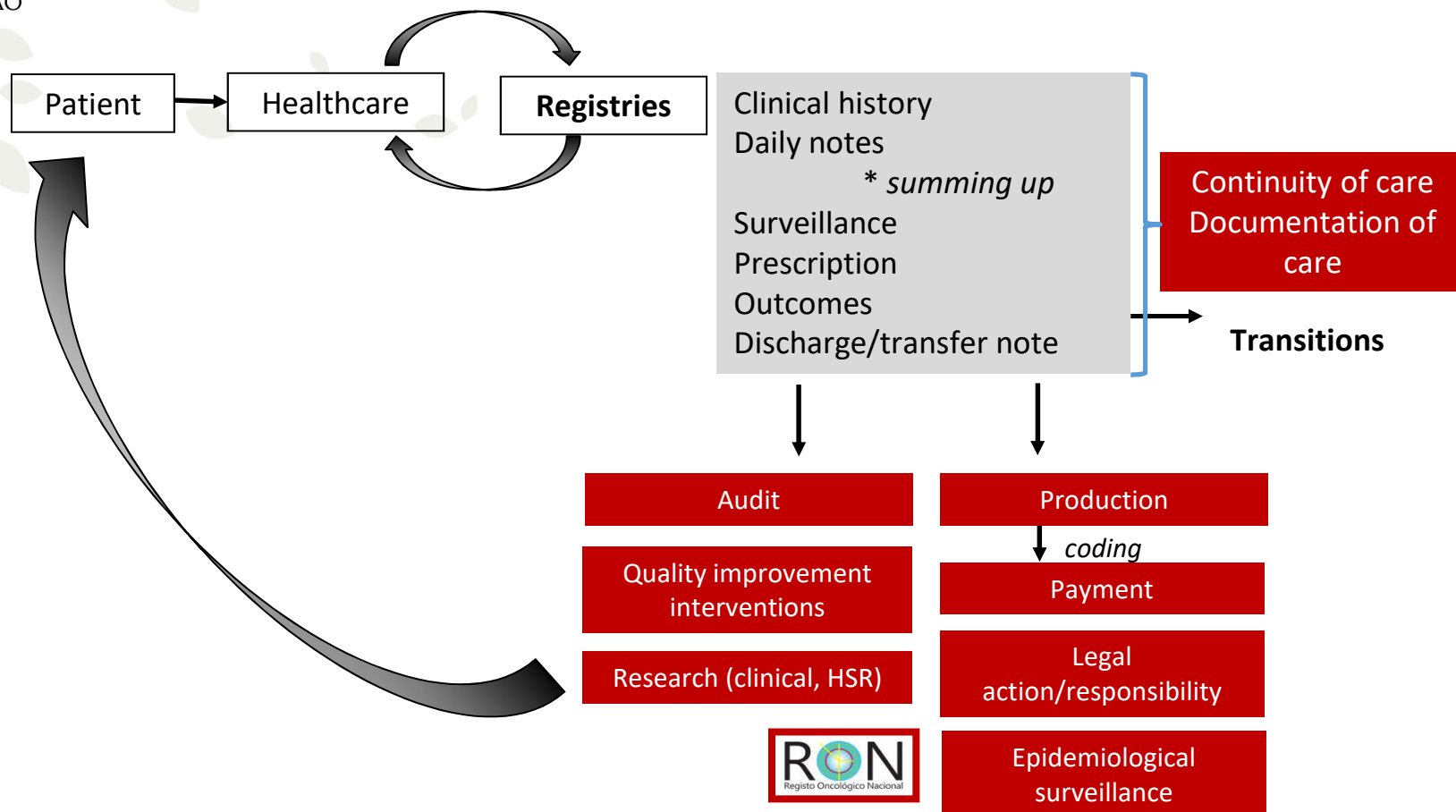
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13 Dec 2022





Spontaneous reporting systems,  
collecting suspected postmarket ADRs with **causality** assessments,  
**are inherently biased.**

## ELECTRONIC CLINICAL RECORD

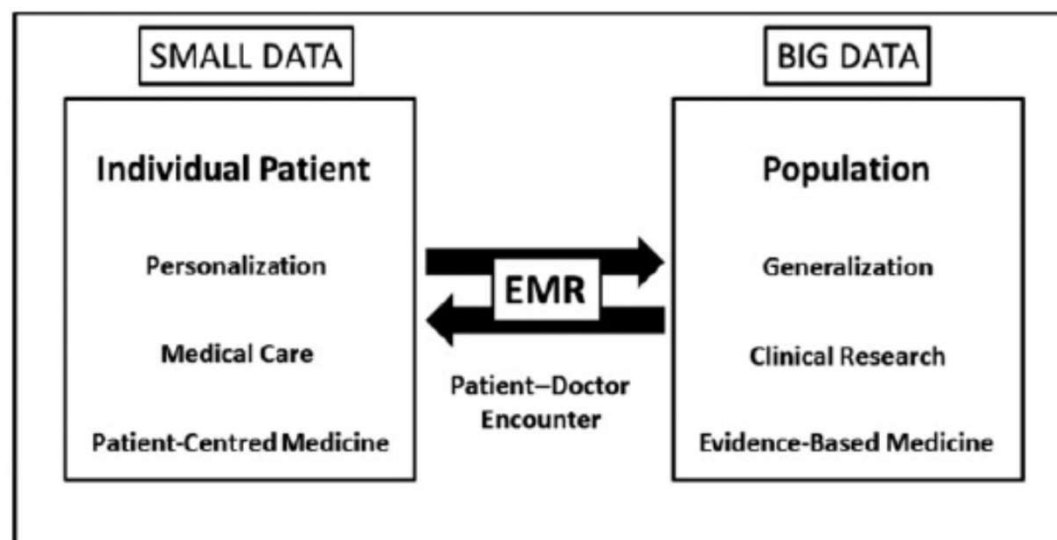




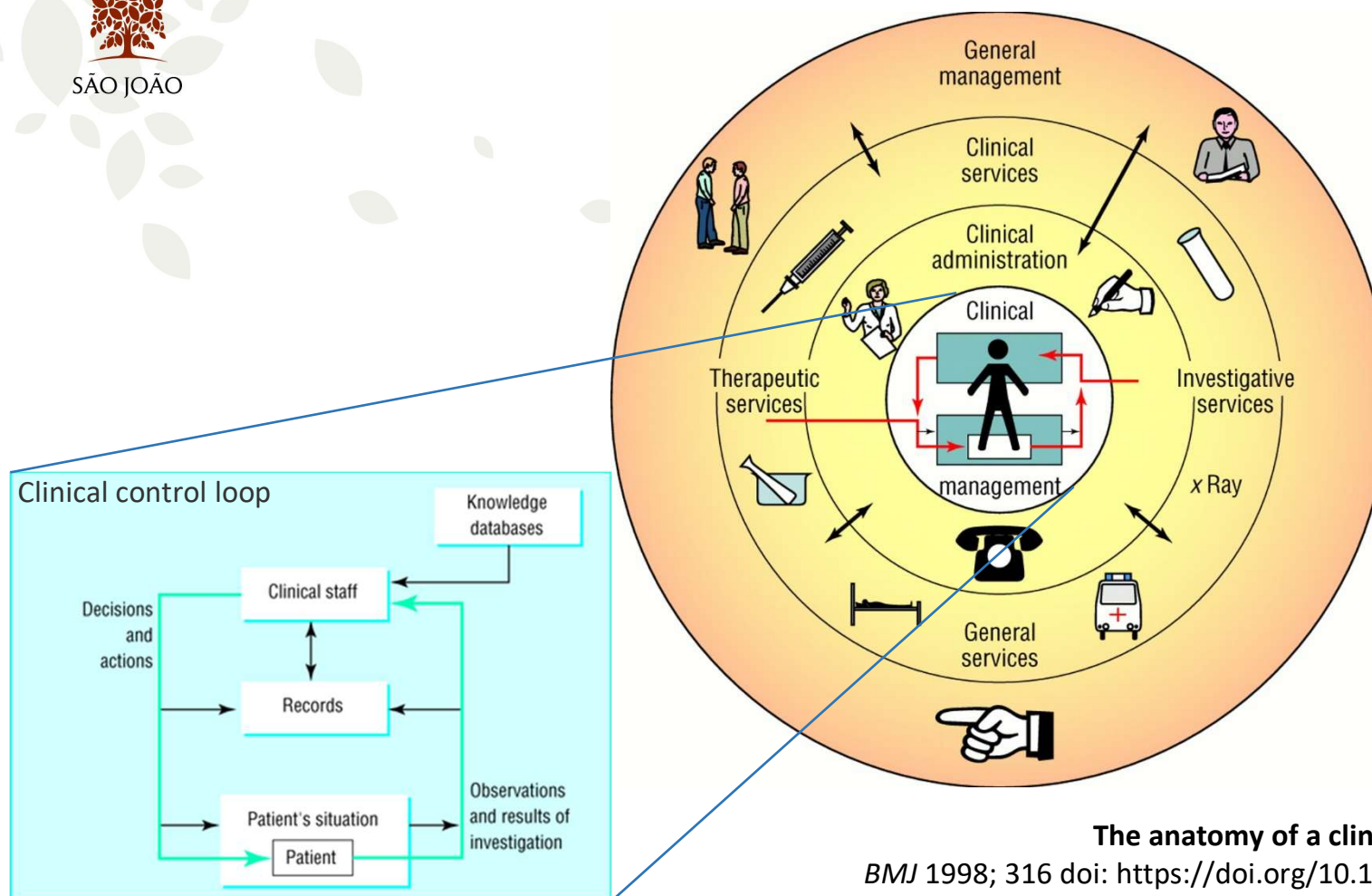
## No big data without small data: learning health care systems begin and end with the individual patient

José A. Sacristán MD PhD<sup>1</sup> and Tatiana Dilla PharmD<sup>2</sup>

### LEARNING HEALTH CARE SYSTEM



**Figure 1** Learning health care system. Each medical act is the intersection between the small and big data.



### The anatomy of a clinical information system

BMJ 1998; 316 doi: <https://doi.org/10.1136/bmj.316.7145.1655>

# HEALTH INFORMATION SYSTEM



# Big Data as secondary data

## Sources

- EHRs (diagnosis, lab results, procedures, medical notes)
- Aggregated clinical trials data
- Administrative health care
- Registries
- Genomics and other -omics data
- Health insurance
- E-health services







## Applications for Big Data in Healthcare



### Diagnostics

Data mining and analysis to identify causes of illness



### Preventative medicine

Predictive analytics and data analysis of genetic, lifestyle, and social circumstances to prevent disease



### Precision medicine

Leveraging aggregate data to drive hyper-personalized care



### Medical research

Data-driven medical and pharmacological research to cure disease and discover new treatments and medicines



### Reduction of adverse medication events

Harnessing of big data to spot medication errors and flag potential adverse reactions



### Cost reduction

Identification of value that drives better patient outcomes for longterm savings



### Population health

Monitor big data to identify disease trends and health strategies based on demographics, geography, and socio-economics



# Electronic health records in research

Type	Example	Status
Observational studies	Health utilization Drug utilization Epidemiology (incidence/prevalence) Natural history Risk factors	Widely used and accepted
Safety surveillance	Traditional post-marketing safety surveillance Active surveillance (e.g., Sentinel <sup>a</sup> )	Widely used and accepted Emerging
Clinical research	Hypothesis generation Feasibility assessments Performance improvement, guideline adherence Patient recruitment Comparative effectiveness, health technology assessments Pragmatic trials (e.g. PROBE design) Point of care randomization Registry randomized trials to test new interventions	Accepted Accepted Accepted Emerging Emerging Emerging Emerging Emerging
Regulatory	Source data to populate eCRF (eliminating or minimizing need for data extraction/data entry) Endpoint or SAE ascertainment Safety surveillance, pharmacovigilance New indications or marketing authorization	Emerging/potential Emerging/potential Accepted Potential

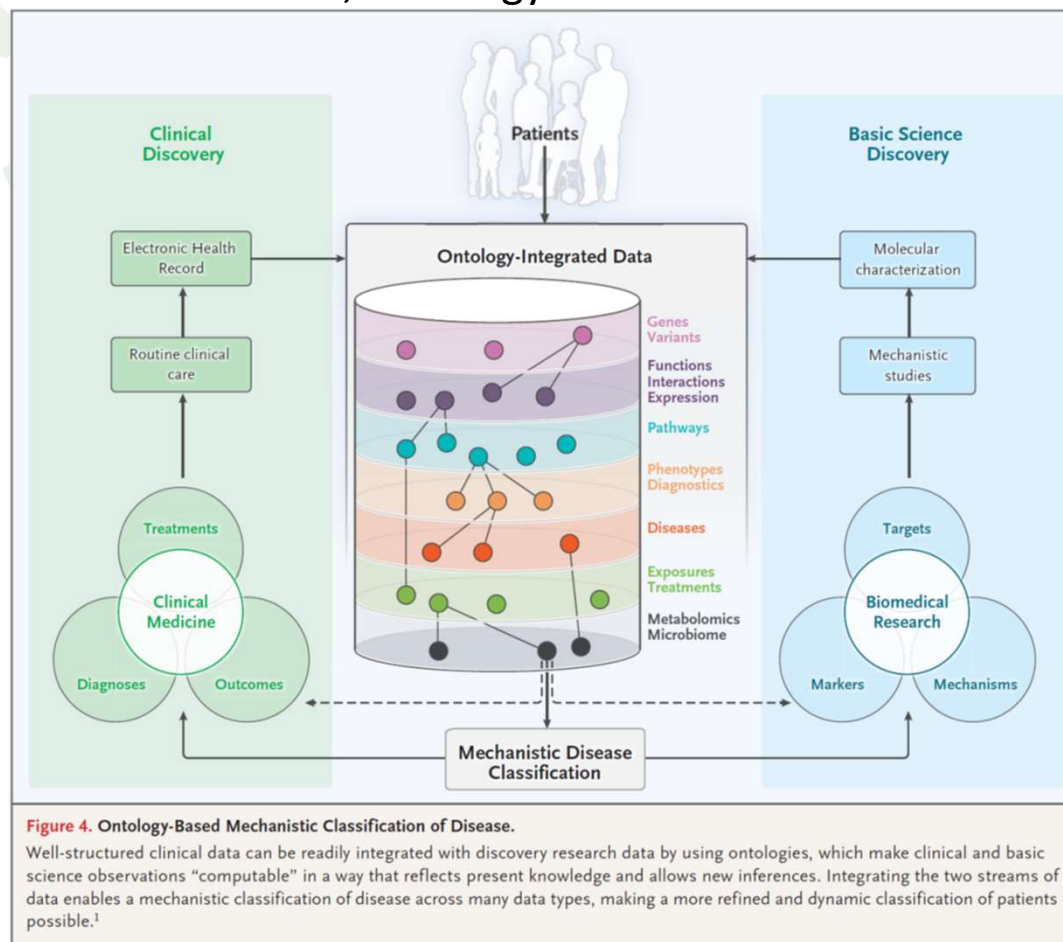
<sup>a</sup> Sentinel is the United States Food and Drug Administration's national electronic system to proactively monitor medical product safety post-marketing, through rapidly and securely accessing data from large amounts of electronic healthcare records, insurance claims, and registries, from a diverse group of data partners [24]

PROBE prospective randomized open blinded endpoint, eCRF electronic case report form, SAE serious adverse event

(pharmacovigilance) AND (electronic health record OR medical record)	N=635
(pharmacovigilance <b>OR drug adverse effects</b> ) AND (electronic health record OR medical record)	N=14766
(pharmacovigilance OR drug adverse effects <b>OR adverse drug reactions</b> ) AND (electronic health record OR medical record)	N=15757
(pharmacovigilance OR drug adverse effects OR adverse drug reactions) AND (electronic health record OR medical record <b>OR real-world data</b> )	N=19400
(pharmacovigilance OR drug adverse effects OR adverse drug reactions) AND (electronic health record OR medical record <b>OR health information system</b> )	N=20942
(pharmacovigilance OR drug adverse effects OR adverse drug reactions) AND (electronic health record OR medical record <b>OR real-world data OR health information system</b> )	N=24504
(pharmacovigilance OR drug adverse effects OR adverse drug reactions) AND (electronic health record OR medical record OR health information system) <b>AND database integration</b>	N=231
(pharmacovigilance OR drug adverse effects OR adverse drug reactions) AND (electronic health record OR medical record) AND database integration	N=142

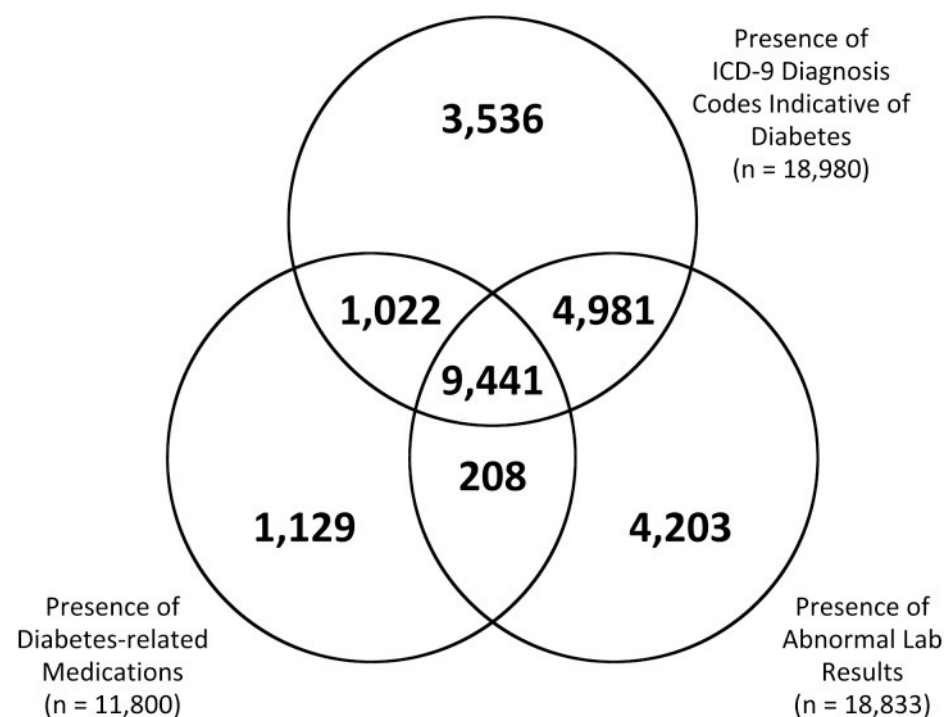


## Classification, Ontology and Precision Medicine





## Quality of data: accuracy and completeness of records



Overlap of diabetes cohorts identified from different categories of phenotype eligibility criteria; n=24 520 patients identified by criteria from any of the three categories



Table II. Positive predictive value (PPV) (effectiveness) of the triggers applied to identify adverse drug reactions (ADRs) in patient records of hospitalized patients.

Trigger	No. of Times the Trigger Was Detected	No. of Times the Trigger Was Associated With an ADR	PPV
INR > 6	12	9	0.75
Abrupt medication stop	271	201	0.74
Serum glucose < 50 mg/dL	29	21	0.72
Sodium polystyrene	28	18	0.64
Rash	33	18	0.55
Fall, lethargy, somnolence	97	50	0.52
WBC count < 3000/mL	21	10	0.48
Creatinine > 1.2 mg/dL	291	29	0.10
Transfer to higher level of care	55	0	0.00
Total	837	356	0.43

INR = international normalized ratio; WBC = white blood cell.

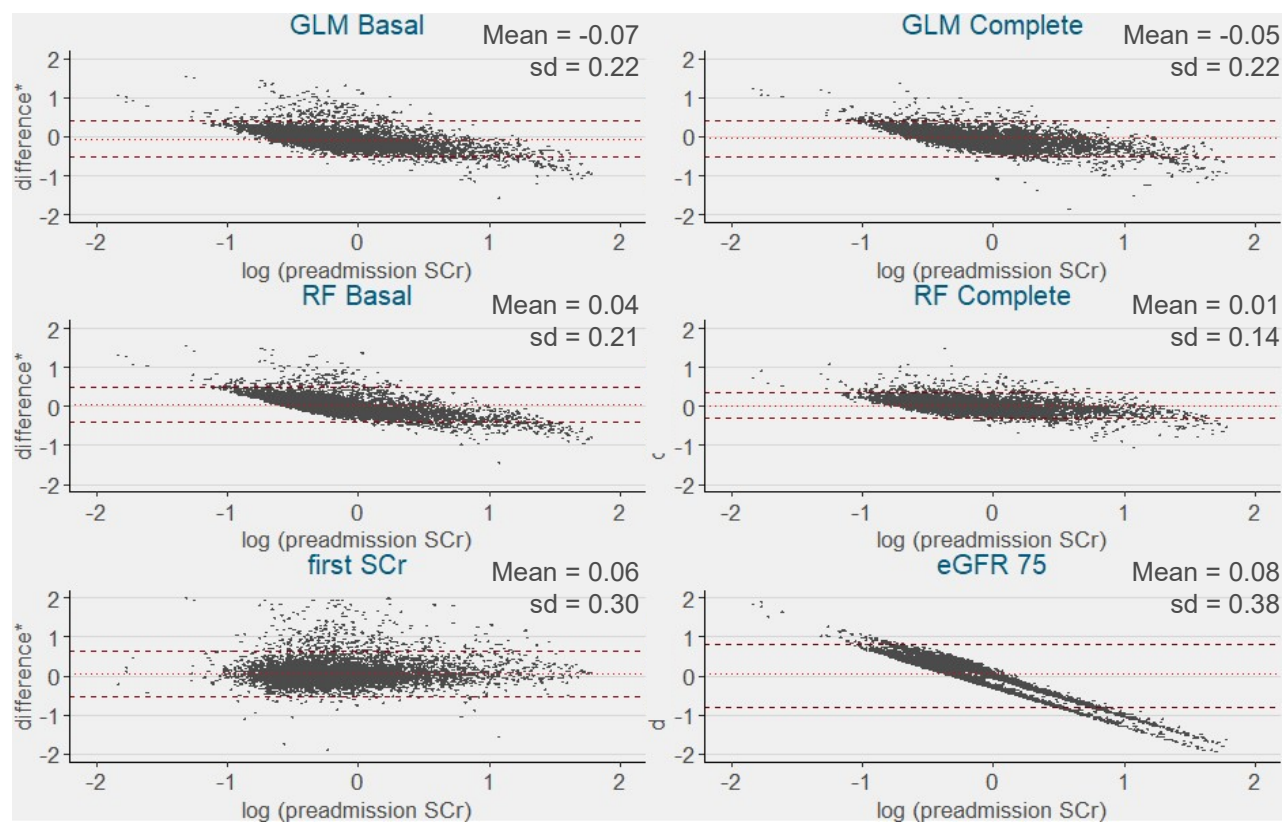


Table III. Drug classes and main confounding variables associated with each of the 9 triggers used in the study.

Trigger	Drug Classes Mainly Associated	Confounding Variables
INR >6	Anticoagulants: warfarin, enoxaparin, heparin	Clinical conditions: hepatic impairment (n = 2) Laboratory test errors (n = 1)
Sodium polystyrene	ACE inhibitors: enalapril Anticoagulants: heparin, enoxaparin, warfarin Potassium-sparing diuretics: spironolactone Cardiotonics: digoxin	Clinical condition: hyperkalemia secondary to renal impairment (n = 10)
Fall, lethargy, somnolence	Drugs that act in the nervous system, with severely enhanced sedation after associated with drugs such as: Neuroleptics: haloperidol, risperidone Anxiolytics: lorazepam, diazepam Hypno-analgesics: morphine	Secondary to worsening patient conditions (n = 40) Sedation scheme (n = 7)
Transfer to a higher level of care	-	Worsening of clinical conditions (n = 55)
Rash	Antibiotics: amoxicillin, azithromycin, clindamycin; pyrazinamide, ciprofloxacin	Mechanical or bacterial phlebitis (n = 3) Clinical conditions (n = 8) Skin infections (n = 4)
Abrupt medication stop	Psychotropic medication Insulin Diuretics: furosemide and spironolactone ACE inhibitors: enalapril Anticoagulants: heparin, enoxaparin, warfarin Antibiotics	Improvement of clinical condition/clinical observation (n = 52) Absence of benefit (n = 18)
WBC <3000 × 10 <sup>6</sup> /μL	Antivirals: aciclovir	Clinical conditions (n = 11)
Serum glucose <50 mg/dL	Insulin: intermediate-acting, fast-acting, regular	Prolonged fastening (n = 5) Clinical conditions (n = 3)
Serum creatinine >1.2 mg/dL	ACE inhibitors: captopril, enalapril Diuretics: furosemide	Acute renal failure with a prerenal component (n = 253) Acute renal failure with a postrenal component (n = 9)



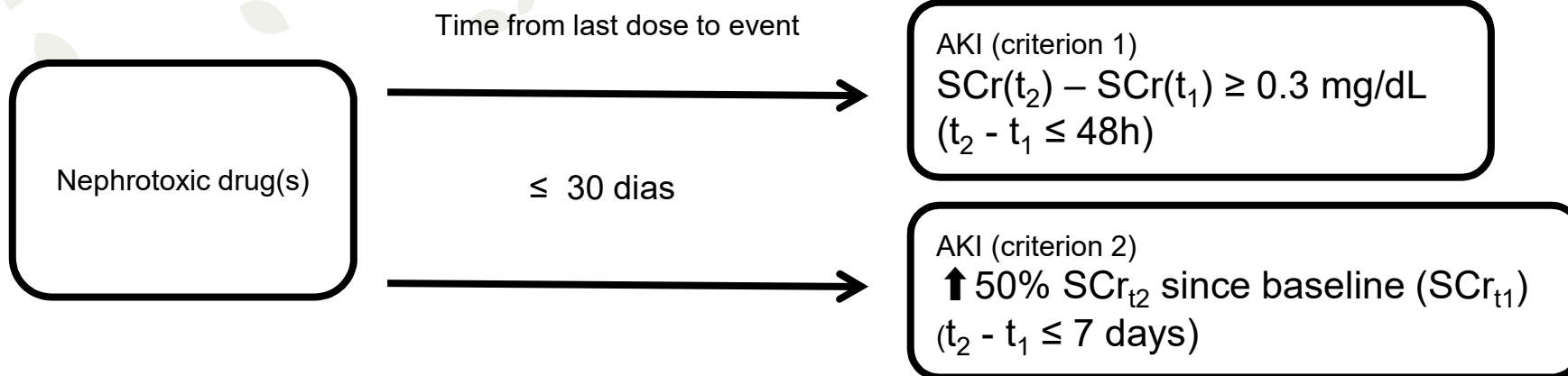
## Comparative assessment of estimation methods for missing baseline SCr value for AKI diagnosis



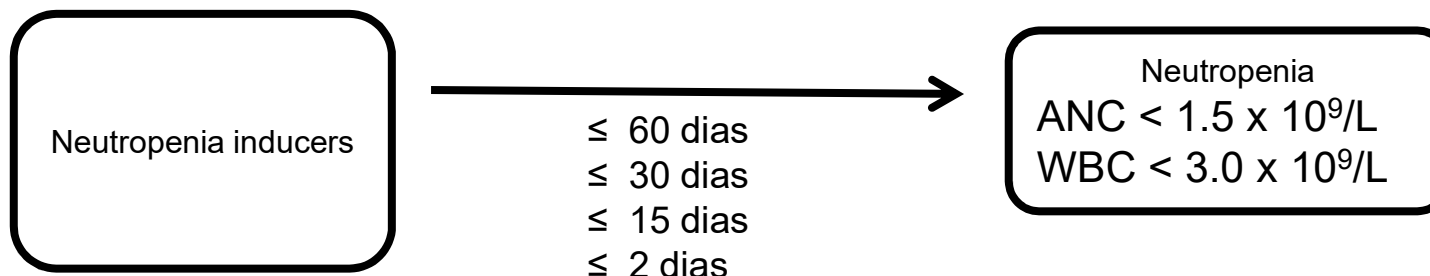
\*differences between log estimated and log known preadmission serum creatinine



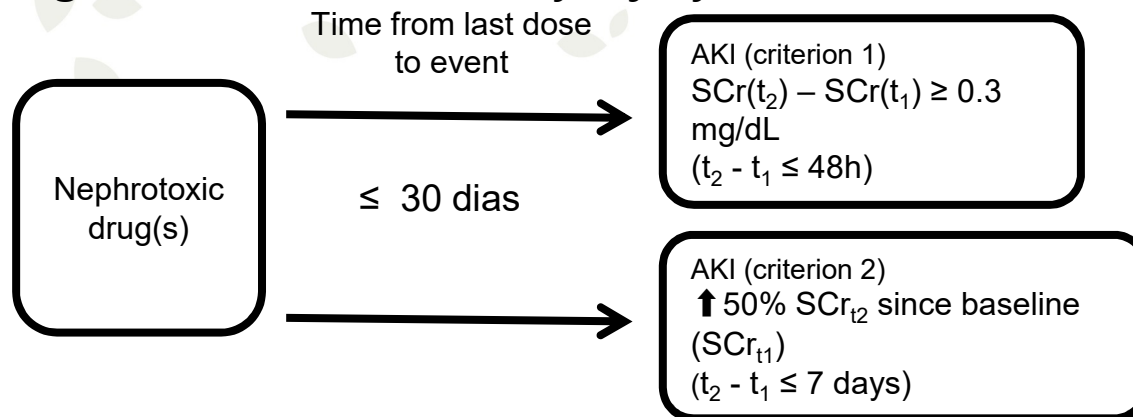
## Drug-induced Acute Kidney Injury (AKI)



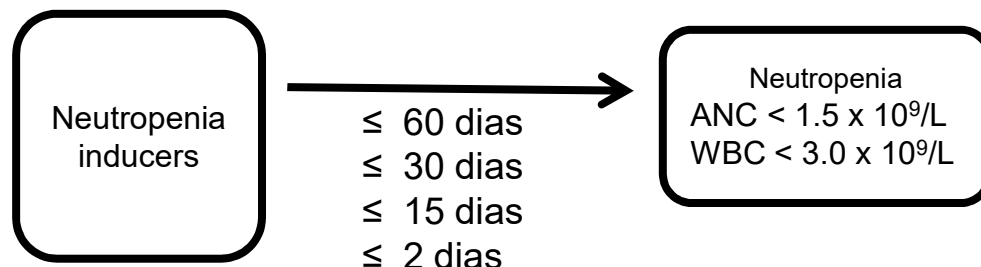
## Drug-induced Neutropenia (DINP)



## Drug-induced Acute Kidney Injury (AKI)



## Drug-induced Neutropenia (DINP)



**Medical record  
review by clinical  
pharmacologists**

**Causality (Naranjo)**



## Possible cases of ADE

Type of ADE / criteria / temp.cutoff	N. of Hospitalizations w/ at least 1 ADE
Drug-induced AKI (criterion: 48 hr )	2,618
Drug-induced AKI (criterion: 7 days)	3,337
Drug-induced AKI (both criteria 48h and/or 7days)	4,195
<hr/>	
Drug-induced Neutropenia (60 days)	961
Drug-induced Neutropenia (30 days)	944
Drug-induced Neutropenia (15 days )	883
Drug-induced Neutropenia (2 days)	378

SAC

http://sclinico2.chsj.min-saude.pt:9001/forms/frmservlet?config=sclinico

Procurar...

Sclinico\_2

Notificar reação - INFARMED, I.P.

Notificar reação - INFARMED, I.P.

Janela

Internamento: Dr(a). Ana Azevedo

Alergias - Dr(a). Ana Azevedo

Sair Salvar RAM

Doente

Teste Chusj Cpat - Adulto (82 anos) Proc: 60018743

Notificar Reações Medicamentosas

Filtrar Todos

Sem conhecimento de ...

Data	Origem	Categoria	Alergénio/agente	Reação	Gravidade
03-03-20	Médico	Alergia medicamentosa	Ibuprofen	Dermatite atópica	Ligeiro
16-02-20	Imunoalergologista	Reação alérgica	Adesivos	Outra	Ligeiro
10-02-20	Imunoalergologista	Alergia alimentar	Outro Alergénio Alimentar	Outra	Ligeiro
07-01-20	Médico	Alergia medicamentosa	Blood And Related Products	Angioedema	Grave
26-10-20	Médico	Alergia medicamentosa	Acamprosate	Broncospasmo	Grave
26-10-20	Médico	Alergia medicamentosa	Acamprosate	Broncospasmo	Grave
27-09-20	Médico	Alergia alimentar	Trigo	Diarreia	Ligeiro
02-09-20	Imunoalergologista	Intolerância medicamentosa	Blood And Related Products	Artrite	Ligeiro
10-08-20	Médico	Alergia medicamentosa	Benzyl Benzoate [ Acarilbial ]	Angioedema	Grave
10-08-20	Imunoalergologista	Alergia medicamentosa	Abacavir	Broncospasmo	Grave
10-08-20	Imunoalergologista	Alergia medicamentosa	Acetylsalicylic Acid [ AAS 150 ]	Broncospasmo	Grave
17-03-20	Imunoalergologista	Alergia medicamentosa	Combinations Of Penicillins	Anafilaxia	Ligeiro

Ativos Ativos Confirmados Ativos Não Confirmados Inativos Inativos Confirmados Inativos Não Confirmados

Dados do registo	Nome do profissional	Estado
17, Novembro 2022	1Enf(a). Sílvia Queiros	Inativo Confirmado
17, Novembro 2022	1Enf(a). Sílvia Queiros	Inativo Não Confirmado
17, Novembro 2022	1Enf(a). Sílvia Queiros	Inativo
03, Março 2022	11:35Enf(a). Cecília Alves	Ativo

Observações

Detalhe Médico | Alergia medicamentosa | Ibuprofen | Dermatite atópica | Ligeiro



SClinico\_2

Notificar reação - INFARMED,...



**Portal RAM**  
Notificação de Reações Adversas  
a Medicamentos

## Notificação de reações adversas/efeitos indesejáveis de medicamentos

Bem-vindo ao Portal de notificação de suspeitas de reações adversas a medicamentos (PORTAL RAM) do Sistema Nacional de Farmacovigilância (SNF).

Neste Portal pode notificar qualquer suspeita de reações adversas a medicamentos.

Este site utiliza cookies. Ao carregar em "Aceitar", está a consentir a sua utilização. Poderá saber mais acedendo à nossa página sobre utilização de cookies.

Aceitar



**HER+** HEALTH EVENT & RISK MANAGEMENT

RISI

Incidentes

Registo de Incidentes

Registo de Incidentes

Lista de Incidentes

Análise

Utilizador: Ana Oliveira

Empresa: Centro Hospitalar Universi...

Sair

Procurar Incidente

TIPO DE INCIDENTE:

Tipos de Ocorrência

1 - Gestão do Percurso do Doente (Processo Assistencial)

2 - Procedimento Clínico/Prestação de Cuidados

3 - Documentação / Informação de saúde

5 - Fármacos/Fluidos Intra-venosos

5A - Reação Adversa a Medicamentos - atualizado

6 - Sangue e Derivados

6A - Reação Transfusional

7 - Alimentação / Nutrição

8 - Gases Medicinais

9A - Dispositivos Médicos/Consumíveis

9B - Equipamentos

10 - Prestação de Serviço de fornecedores externos



HER+ HEALTH EVENT & RISK MANAGEMENT

Registo de Incidentes

Lista de Incidentes

Análise

RISI

Incidentes

Registo de Incidentes

Nº. de Incidente: Novo Estado: Aberto Tipo de Incidente: 5A - Reação Adversa a Medicamentos - atualizado

Tratamento de Informação e Confidencialidade dos Dados

Aviso:  
Para poder notificar uma reação adversa, é necessário fornecer alguns dados pessoais para que seja possível contactá-lo, caso haja necessidade de esclarecimentos adicionais relativamente à mesma.  
As informações fornecidas serão mantidas seguras e confidenciais, e não serão partilhadas com entidades externas ao Sistema Nacional de Farmacovigilância.  
(Deve ser seleccionada pelo menos uma opção, das assinaladas com \*)  
☐ Confirmo que li e compreendi o texto em cima \*

Submissão (preenchido automaticamente pelo INFARMED)

Nº de submissão

Data de submissão

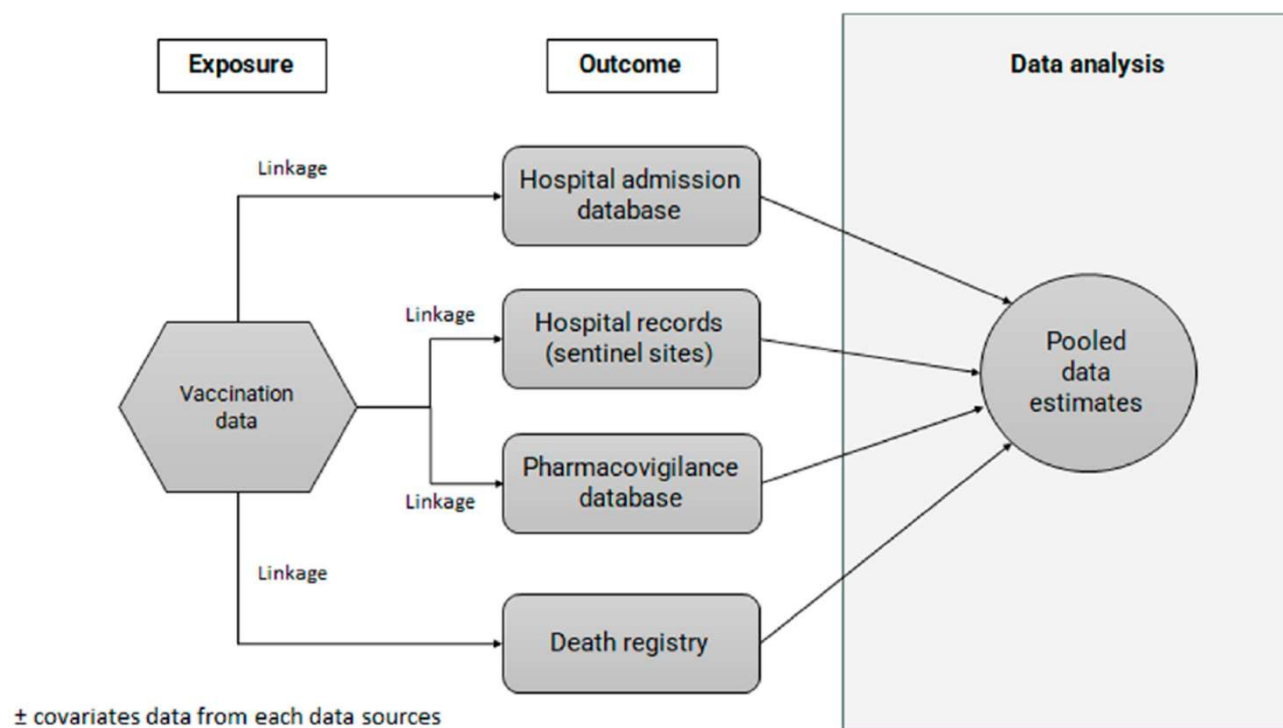
Erro (no caso de falha de comunicação com o Infarmed)

EVIDÊNCIAS (FOTOS, DOCUMENTOS), SE NECESSÁRIO

DESCRIÇÃO

DATA DE CRIAÇÃO

UTILIZADOR DE CRIAÇÃO



**FIGURE 1 |** Linkage of data sources for establishment of study cohort.

A Case-Based Monitoring Approach to Evaluate Safety of COVID-19 Vaccines in a Partially Integrated Health Information System: A Study Protocol. Front. Pharmacol. 13:834940. doi: 10.3389/fphar.2022.834940





## In conclusion

- Best encounter between protocol and purpose
- Selection bias/representativeness + meaning in context/datasource + confounding
- Scientific/clinical interpretation *versus* technological possibilities

**Plead for a role of epidemiology in  
design and implementation of integration solutions**



SNS SERVIÇO NACIONAL  
DE SAÚDE

# Obrigado(a)

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