Developing a Comprehensive Framework for Real-World Data Validation in Vaccine Safety Monitoring: The VAC4EU experience

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Validate study variables to reduce misclassification bias: recent tools and research needs

HYBRID WORKSHOP

27 March 2025 - 14.30-18.30

ARS Toscana - Villa La Quiete, via Pietro Dazzi 1 - Florence, Italy

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NETWORK

Our Data Sources

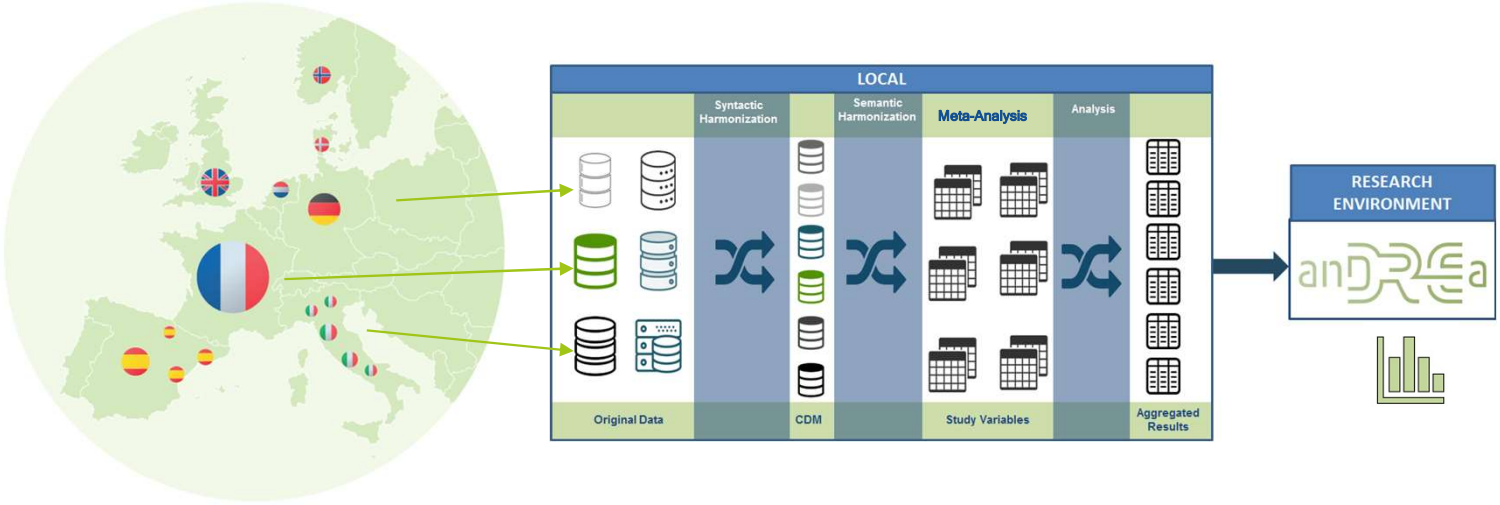
- **16 Real World Data sources** across our network
- Approximately **152 million individuals** covered
- Types of data include but are not limited to:
  - Record linkage
  - GP medical records
  - Hospital records
  - Claims data

VAC4EU RWE STUDIES

Distributed Approach

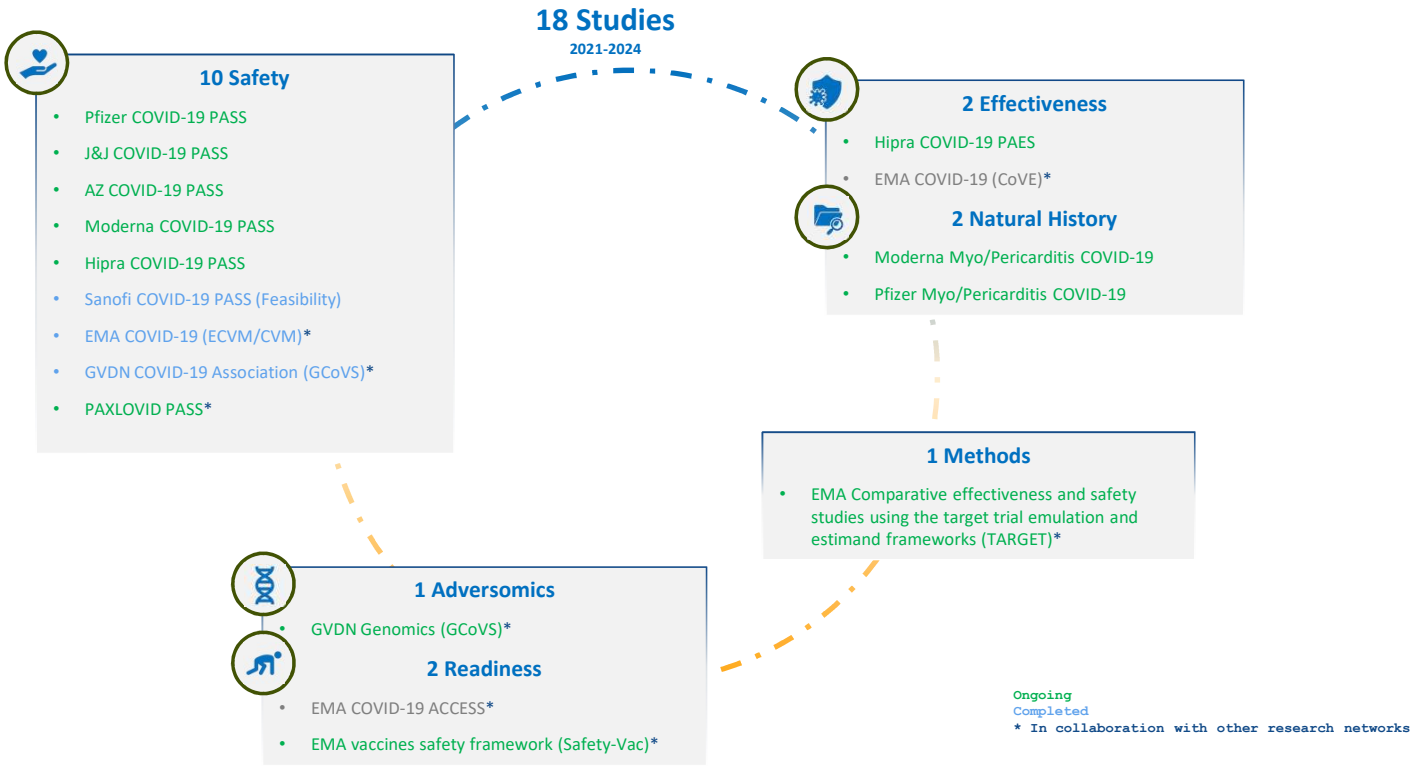
VAC4EU study teams use a **common protocol**, **common data model** (CDM), and **common analytics programs**.

Data stay local at DEAPs level



VAC4EU STUDIES

Portfolio



Introduction

Case validation in VAC4EU studies

VAC4EU aims to produce best quality evidence on vaccine effects from RWD

In line with FDA guidance and EMA/ENCePP guidance validation of core outcomes is conducted for PASS.

VAC4EU uses Brighton Collaboration case definitions as the basis for outcome validation (if they exist)

VAC4EU has a coordinator for validation and a validation task force (coordinator and medically trained delegates of study teams)

VAC4EU validation task force: **Amirreza Dehghan Tarazjani (VAC4EU), Alejandro Arana (RTI), Miriam Sturkenboom (UMCU), Daniel Weibel (VAC4EU), Fariba Ahmadizar (UMCU), Joan Fortuny (RTI, Cristina Rebordosa (RTI), Laura Zwiers (Julius Clinical)**

VAC4EU Validation Workflow

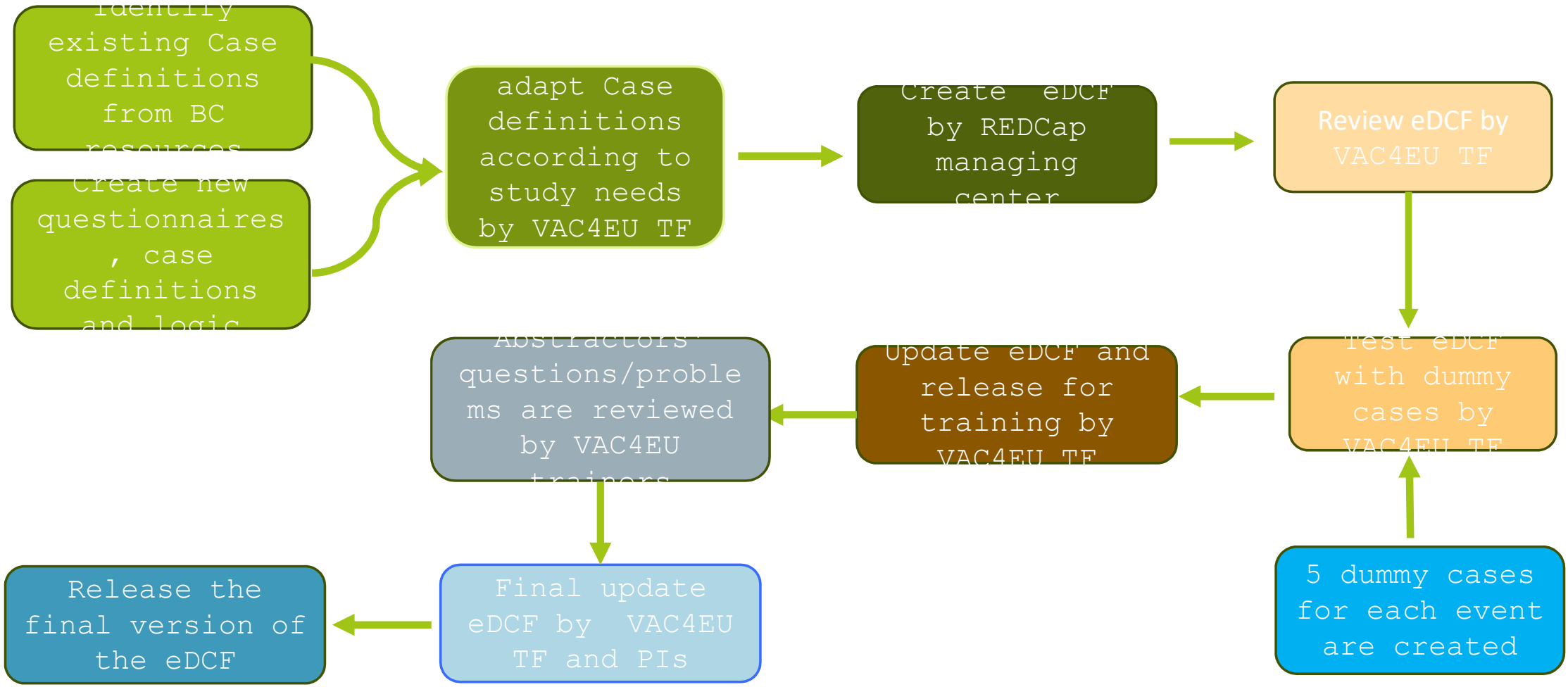
- Includes three main steps:

1. Creating the case definition

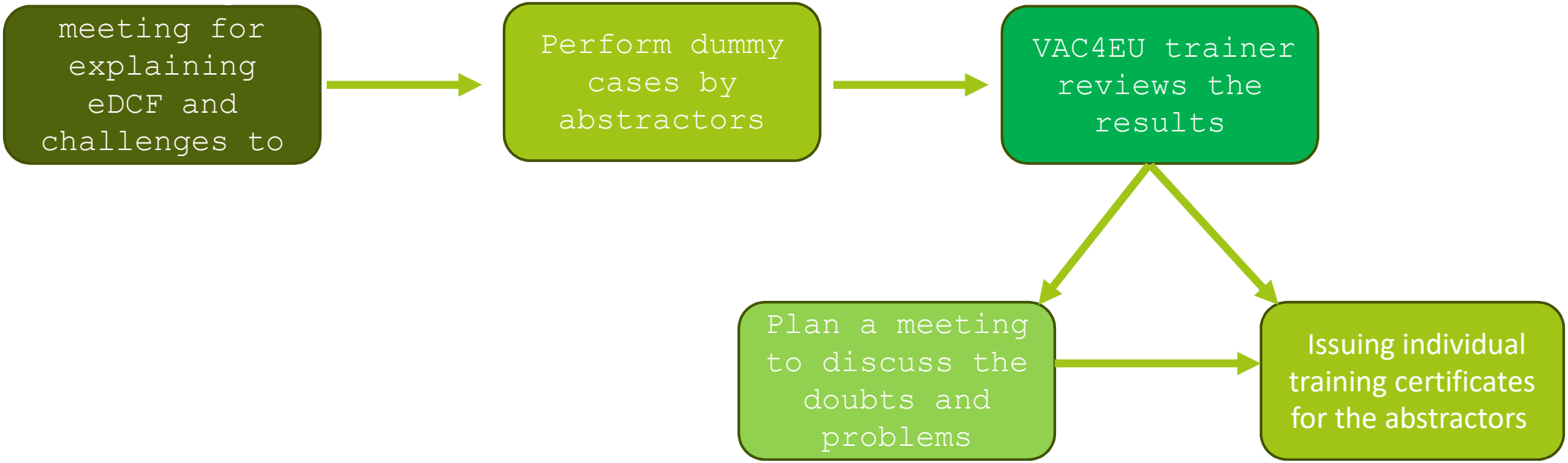
2. Creating electronic Data Capture Form (eDCF) using REDCap

3. Training abstractors

Creating case definition and eDCF



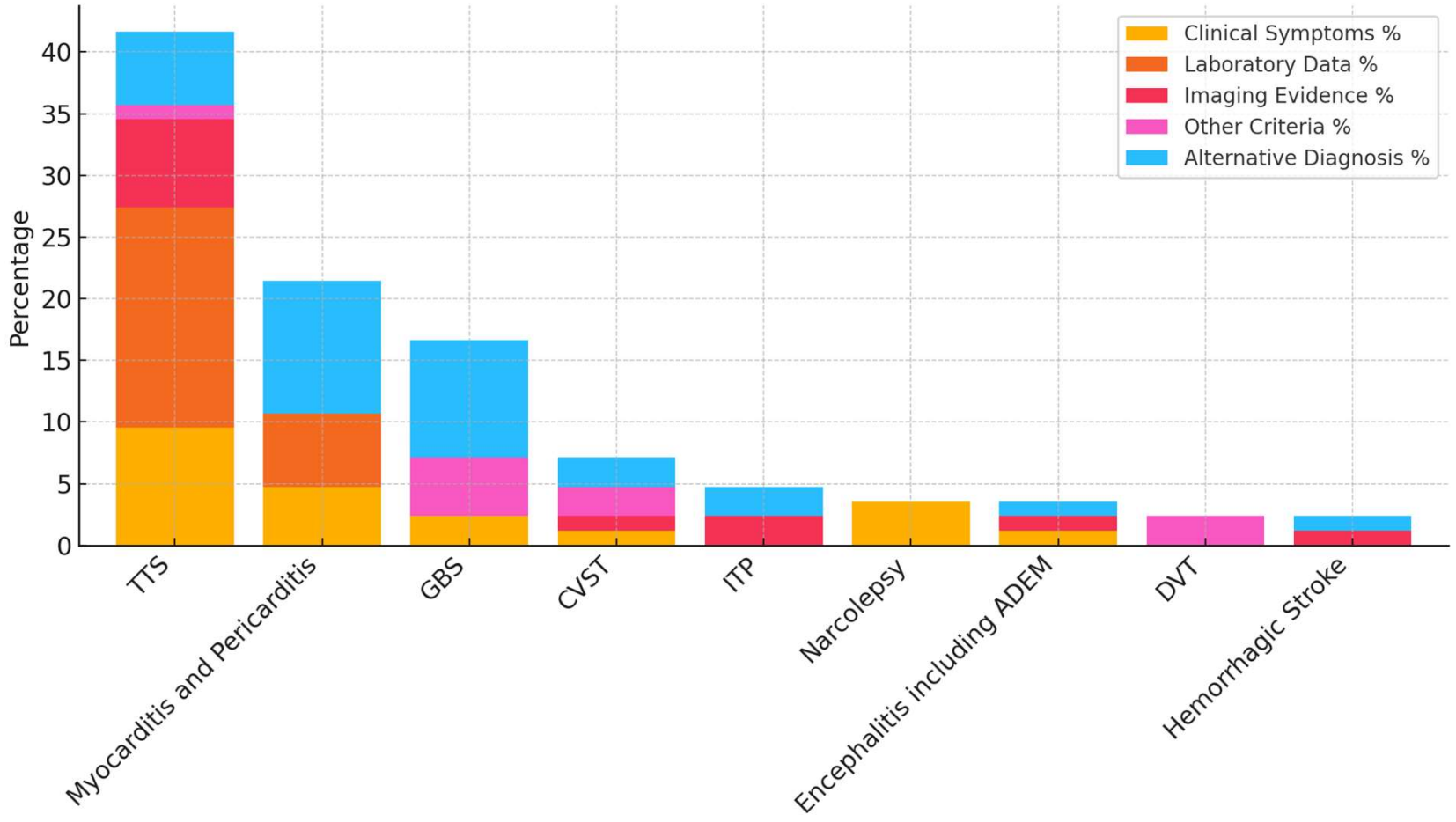
Training Workflow



The distribution of discrepancies across abstracted dummy cases in the training

Events	Abstractors	Abstracted dummy cases	Discrepancies: Abstractor vs. Expected (%)	Fleiss' Kappa (Confidence Interval)
GBS	13	65	21.5%	0.363 (0.002,0.723)
Narcolepsy	13	65	4.61%	0.476 (0.370, 0.582)
(Idiopathic) thrombocytopenia	15	75	5.33%	0.475 (0.276, 0.674)
TTS	16	80	53.75%	-0.0527 (-0.4887, 0.3833)
Myocarditis	22	66	11%	0.442 (0.315, 0.569)
Pericarditis	22	66	6%	0.468 (0.258, 0.678)
Transverse myelitis	13	65	0%	1
Encephalitis - including ADEM	5	25	8%	0.456 (0.219, 0.693)
Thrombocytopenia with bleeding	4	20	0%	1
Deep vein thrombosis	5	25	8%	0.456 (0.219, 0.693)
Pulmonary embolism	4	20	0%	1
Hemorrhagic stroke	4	20	10%	0.444 (0.181, 0.707)
Non hemorrhagic stroke	5	25	0%	1
Cerebral venous thrombosis	4	20	15%	0.375 (0.026, 0.724)

Distribution of validation discrepancies across criteria for different events



List of events and number of validated cases in VAC4EU sites as of December 2024

Names of studies	Events/Number of cases													
	GBS	Narcolepsy	ITP	TTS	Myocarditis	Pericarditis	T.M	Encephalitis - including ADEM	DVT	PE	Hemorrhagic stroke	Non hemorrhagic stroke	CVST	Thrombocytopenia with bleeding
Pfizer1021	158	113	342	72	173	490	42	-	-	-	-	-	-	-
Pfizer1038	-	-	-	-	2211	5013	-	-	-	-	-	-	-	-
Janssen and Janssen	12	0	10	115	0	0	3	16	50	50	39	50	12	-
Moderna NatMyo	-	-	-	-	38	-	-	-	-	-	-	-	-	-
AZD1222	-	-	-	76	-	-	-	-	-	-	-	-	-	115

Example : TTS case definition

The Main Challenges Identified by RWD:

- **Establishing a clear definition for "new-onset"**
- **Defining ranges for age-adjusted D-dimer values and calculation**
- **Standardizing ranges and approaches to account for different laboratory units**
- **Simplifying the questionnaire to make it as user-friendly as possible for abstractors**

Adaptation for criteria A

Brightion Version	VAC4EU version
☐ **Platelet count <150 X 109/L and of new-onset with no known recent exposure to heparin (within the last 30 days)**	☐ Platelet count <150 X 10^9/L and of new onset (Maximum 10 days before the first symptom) with no known recent exposure to heparin (within the last 30 days), Platelet count value and unit_____ o Yes o No o Unknown

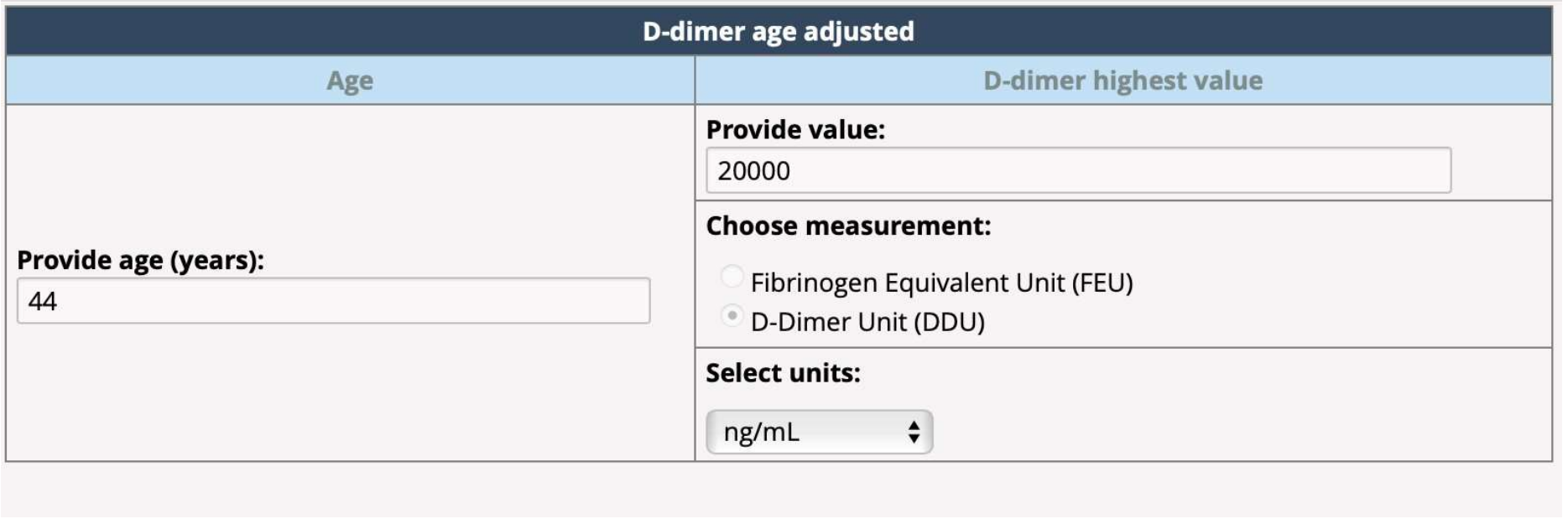
Adaptation for Calculating the D-dimer

Brighton Version	VAC4EU version
Condition B2: Elevated D-DIMER >8x ULN (Upper limits of normal)	D-dimer ≥4000 mcg/L (FEU)
Condition D: Elevated above upper limit of normal	2000 >D-dimer ≥500 mcg/L (FEU)
Condition E: D-dimer > 4 times ULN for age	4000 >D-dimer ≥2000 mcg/L (FEU)

D-dimer Calculation

The main adaptation includes:

Automatically calculate age-adjusted D-dimer values and require abstractors to provide input only once at the start of the form, with the appropriate unit specified.



SPEAC (THE SAFETY PLATFORM FOR EMERGENCY VACCINES) – VAC4EU living lab

SPEAC is a project of the Brighton Collaboration at The Task Force for Global Health, funded by the Coalition of Epidemic Preparedness and Innovations to harmonize vaccine safety monitoring across the vaccine life cycle. In 2024, VAC4EU and SPEAC signed a Memorandum of Understanding to begin collaborating on a Living Lab

The purpose of the living lab collaboration is:

- to devise ways to accommodate the BC Case Definitions for application to RWD settings
- to improve CD life cycle processes (for SPEAC)
- to promote VAC4EU best practices for creation of harmonized global standard (BC CDs)
- to expedite and explain CD adaptations for different RWD platforms
- to train and educate the research communities on BC case definition used for RWD
- to improve Real World Evidence generation across global activities

This will be achieved through:

--> Sharing of experience and content from VAC4EU studies with SPEAC
--> Discuss potential adaptations to BC and/or companion guides
--> Joint publication and dissemination activities.

Discussion

1. How accurate should we be in ensuring that all abstractors classify cases in the same way?

2. Do we need to ensure 100% agreement among abstractors, or is some level of variability acceptable?