Experience of clinical trial conduct: War in Ukraine, one sponsor's perspective

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Background

15 years in clinical trials industry

8 years of monitoring

7 years in quality control and assurance

- process management
- audits and inspections support
- in-house and onsite quality control
- suppliers’ assessment and qualification
- trainings
- privacy & compliance matters
- consultations & innovative solutions

Agenda

- What is business continuity during the war in Ukraine and how do we ensure that no patient is left behind?
- Leading people, process, projects
- Processes adaptation, flexible decisions: remote SDR and SDV implementation
- Experience in patient transfers within and outside of Ukraine

Business Continuity Plan Framework

Where to start?

Team

Leadership Team of MSD Ukraine, Clinical Department

- **Government instructions** (education for emergency)
- **Risk assessment:**
  - identify, assess, mitigate, monitor
- **Map** every direction
  - people – location, safety (global notification system, applications, chats)
  - process – is it working? if no, why not and how to solve?
  - projects – from systemic approach to study-specific
- **Update** procedures:
  - Business Continuity, Incident Management
    - patient transfers
    - medication supplies (logistics, cross-protocols, site-to-site)
- **Document** every process gap, deviations from
  - Protocols
  - SOPs
  - Other established processes
- Constant assessment of regulatory environment

Several risks on country level

Spring 2022

Several risks on department Spring 2022

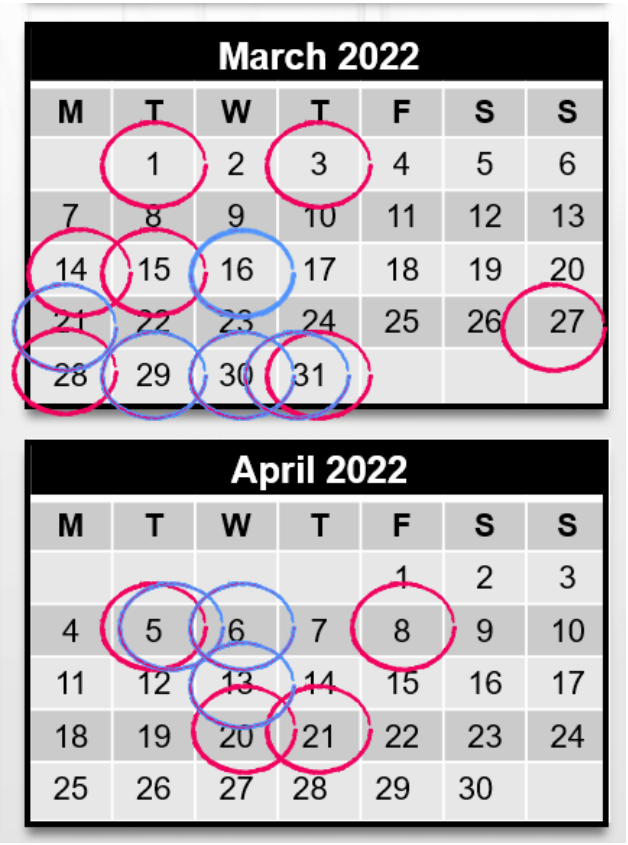
Lessons learned from past years

Business Continuity Plan for COVID-19 leveraged to respond to war

Regulatory Agencies recommendations for COVID-19 were similar

Start of war in 2014 experience from East and South of Ukraine

Regulations update storyboard



Ukrainian regulations updates

International regulations updates

State Expert Center MoH Ukraine

MINISTRY OF HEALTH OF UKRAINE

Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych

BETA

Działając w obszarach produktów leczniczych, wyrobów medycznych i produktów biobójczych chronimy zdrowie i dbamy o bezpieczeństwo społeczeństwa

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

OGYÉI

famhp
federal agency for medicines and health products

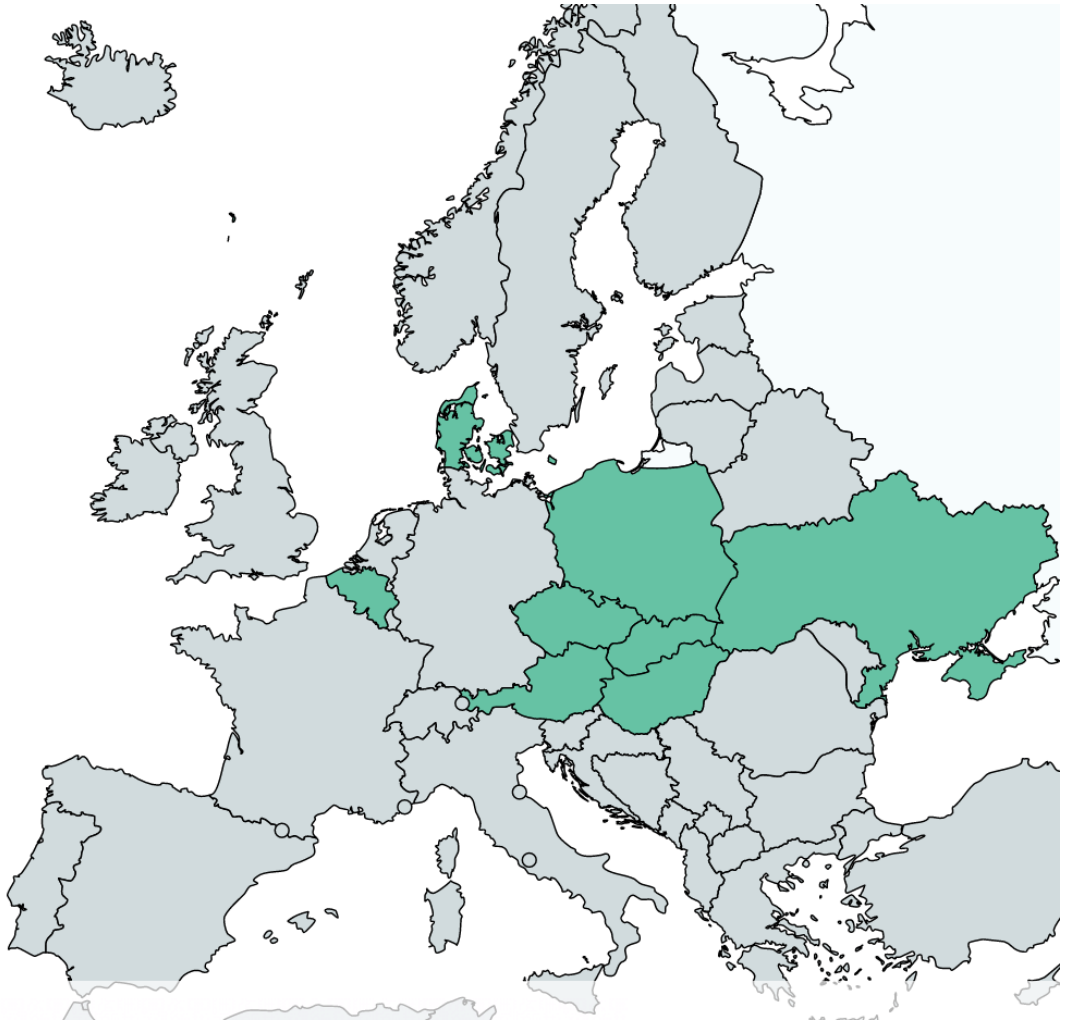
SUKL
State Institute for Drug Control

HMA
Heads of Medicines Agencies

Austrian Federal Office for Safety in Health Care
BASG

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

SÚKL



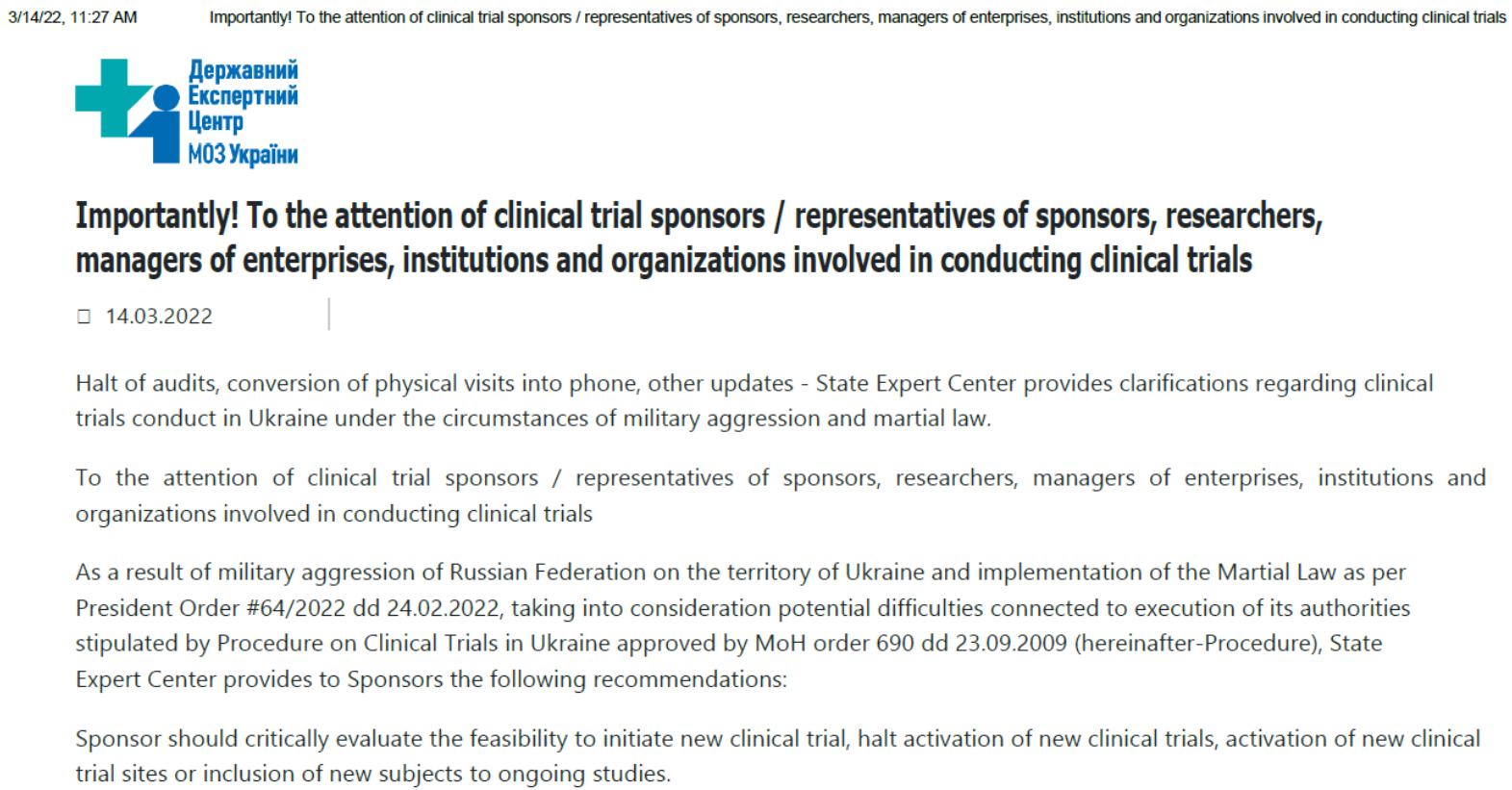
Additional regulations released and assessed for war in Ukraine

Regulatory aspects – beginning of full-scale war (March 2022)

State Expert Center (Ukrainian Regulatory) is constantly updating the requirements to align with European regulations, industry needs and reality.

Basic considerations:

- The regulations developed during the COVID-19 pandemic are applicable in terms of ongoing war
- Audits and inspections were put on hold
- Before starting a new trial or open up/resume a screening the Sponsor should assess each case critically
- Transfers to other countries are possible and UA RA should be notified
- Continue to report protocol violations to UA RA
- Paper submission continue
- Verbal consent possible in certain cases
- Patient visits can be replaced by calls in certain cases
- IP home delivery under certain conditions
- Alternate methods for performing remote, routine SDR/SDV during site access restrictions and should be used in conjunction with UA RA and LECs
- To minimize the burden on the participant, it is recommended to not require separate visits to complete these steps



3/14/22, 11:27 AM Importantly! To the attention of clinical trial sponsors / representatives of sponsors, researchers, managers of enterprises, institutions and organizations involved in conducting clinical trials

Державний Експертний Центр МОЗ України

Importantly! To the attention of clinical trial sponsors / representatives of sponsors, researchers, managers of enterprises, institutions and organizations involved in conducting clinical trials

14.03.2022

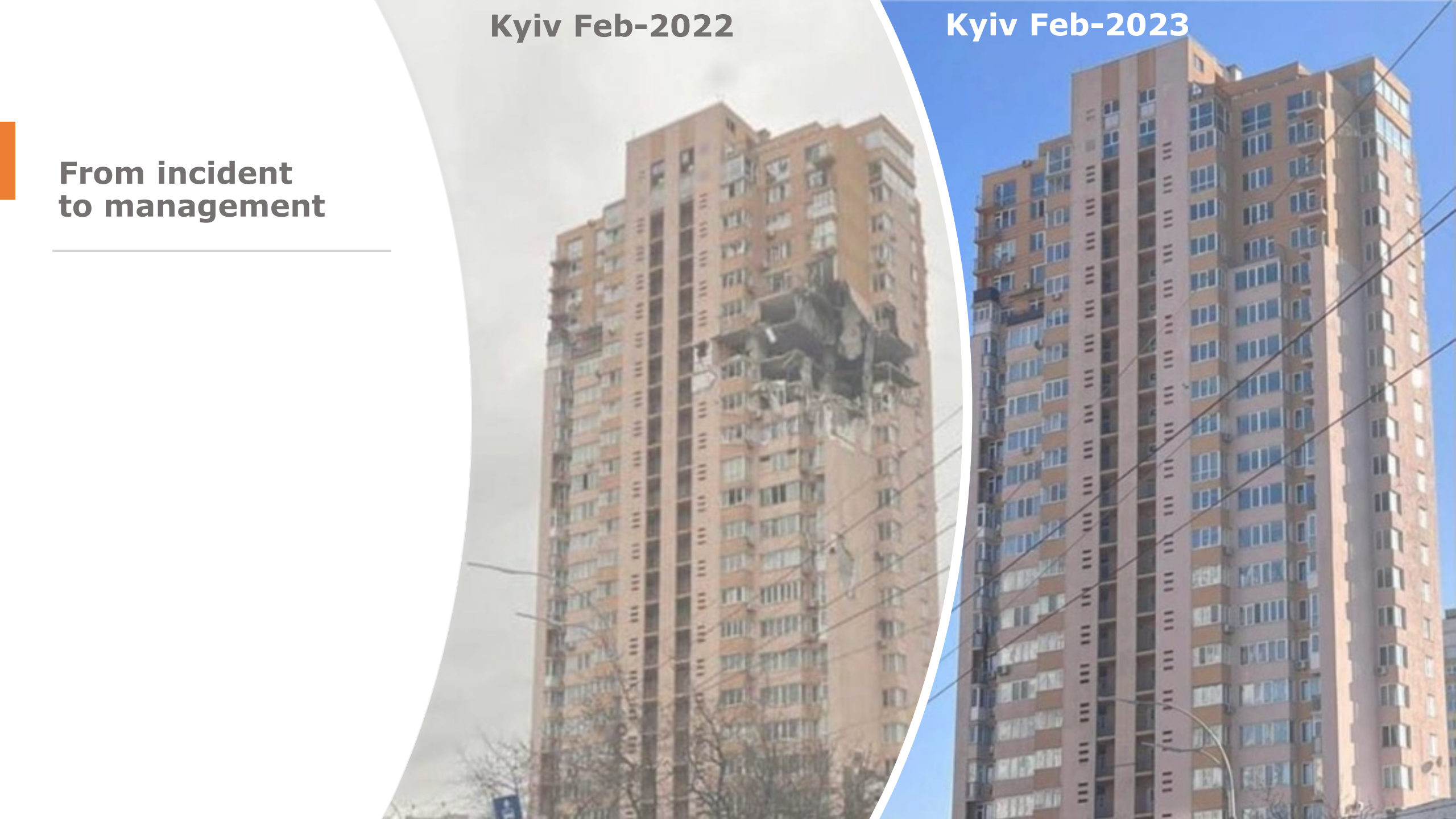
Halt of audits, conversion of physical visits into phone, other updates - State Expert Center provides clarifications regarding clinical trials conduct in Ukraine under the circumstances of military aggression and martial law.

To the attention of clinical trial sponsors / representatives of sponsors, researchers, managers of enterprises, institutions and organizations involved in conducting clinical trials

As a result of military aggression of Russian Federation on the territory of Ukraine and implementation of the Martial Law as per President Order #64/2022 dd 24.02.2022, taking into consideration potential difficulties connected to execution of its authorities stipulated by Procedure on Clinical Trials in Ukraine approved by MoH order 690 dd 23.09.2009 (hereinafter-Procedure), State Expert Center provides to Sponsors the following recommendations:

Sponsor should critically evaluate the feasibility to initiate new clinical trial, halt activation of new clinical trials, activation of new clinical trial sites or inclusion of new subjects to ongoing studies.

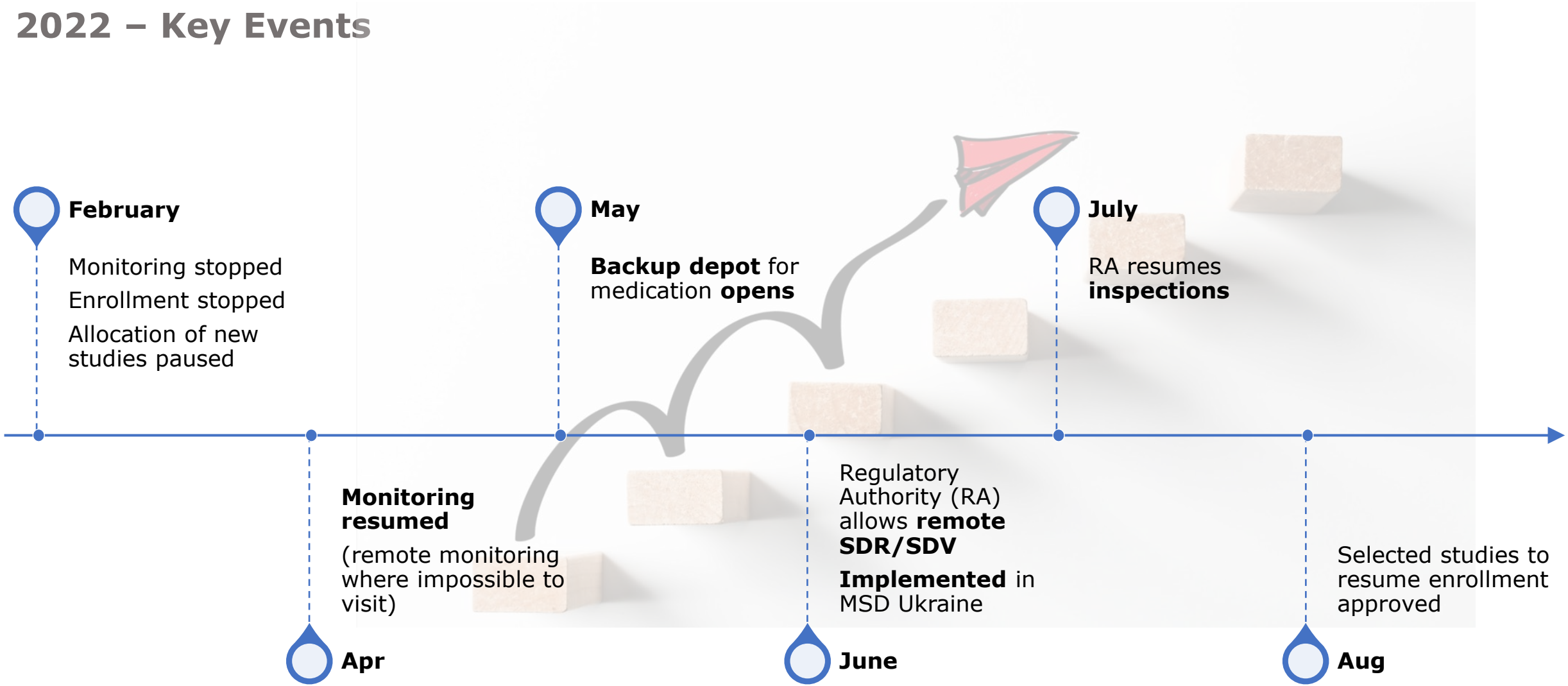
From incident to management



BCP directions

Requirements:	Implementation:
The regulations developed during the COVID-19 pandemic are applicable in terms of ongoing war	Many **processes developed** in 2020 and 2021 to overcome **COVID-19 impact used now too**
The audits and inspections were put on hold	RA announced they are **back to the onsite inspections** in Q2-2022 (3 months after massive attack). Focus – patient transfers (original and receiving sites if safe and logistically possible)
Before starting a new trial or open up/resume a screening the Sponsor should assess each case critically	Senior Management decision on a case-by-case basis
Transfers to other countries are possible and UA RA should be notified	Participant mobility team created (**Triage Team)** to support any transfers abroad or domestic
Continue to report protocol violations to UA RA	Business as usual – submitted in annual report
Paper submission continue	**Electronical pre-submissions possible** via email, paper to follow
Verbal consent possible in certain cases with impartial witness involvement	Mostly not used. Always **followed by the signing ICF in person** after
Patients' visits can be replaced by calls in certain cases	If replaced, a **Protocol Deviation** to be reported
IP home delivery under certain conditions	Procedure used in isolated cases for **oral IP only**. On a separate note: **site-to-site transfers, cross-protocol transfers**
Alternate methods for performing remote, routine SDR/SDV during site access restrictions and should be used in conjunction with UA RA and LECs	Implemented in a full scope at more that 100 sites (Please note that Ukraine does not have general electronic source records, most of SD is paper)

2022 – Key Events



February

Monitoring stopped

Enrollment stopped

Allocation of new studies paused

Apr

Monitoring resumed

(remote monitoring where impossible to visit)

May

Backup depot for medication **opens**

June

Regulatory Authority (RA) allows **remote SDR/SDV**

Implemented in MSD Ukraine

July

RA resumes **inspections**

Aug

Selected studies to resume enrollment approved

Remote SDR/SDV prerequisites

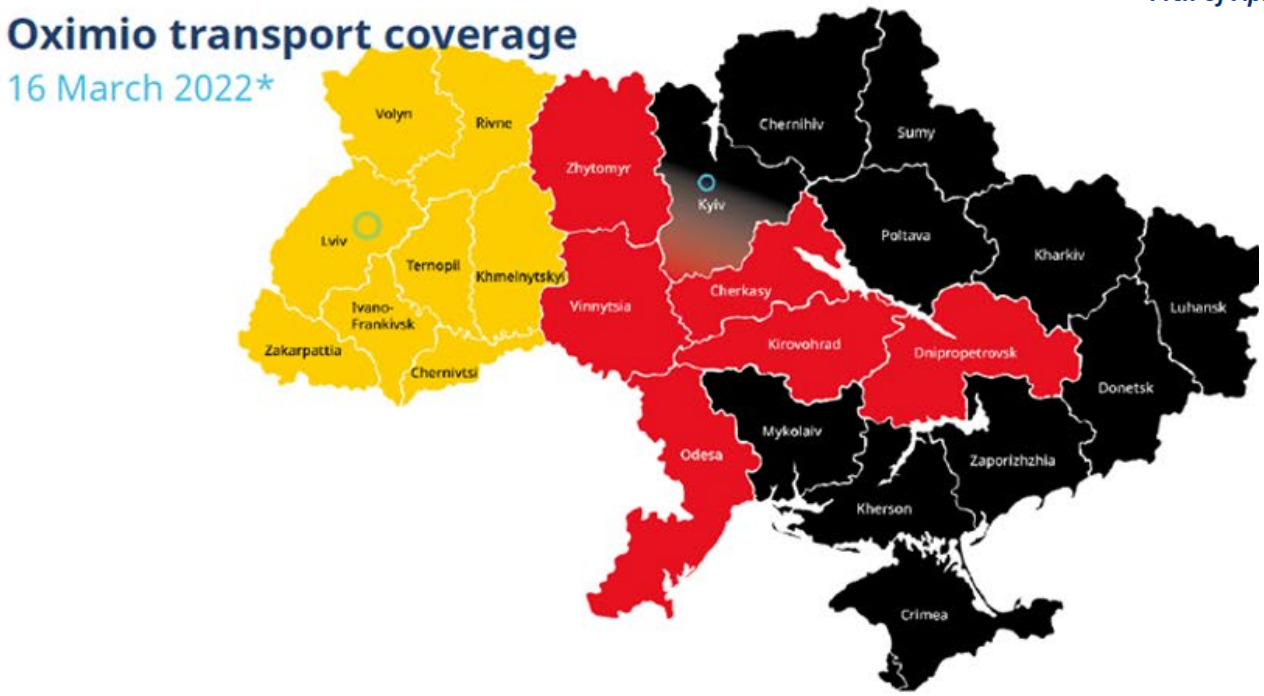
- Regulations allowing approach
- ICF form containing the wording around r-SDR/SDV
- Company's approach supporting r-SDR/SDV
- Site's SOP to use r-SDR/SDV
- Certified copies use (upload to the system/platform)
- Site's will to implement innovation
- Privacy aspects
- Spotcheck of SD when back on site
- Use of only those systems/platforms allowed by the Sponsor and other IT considerations

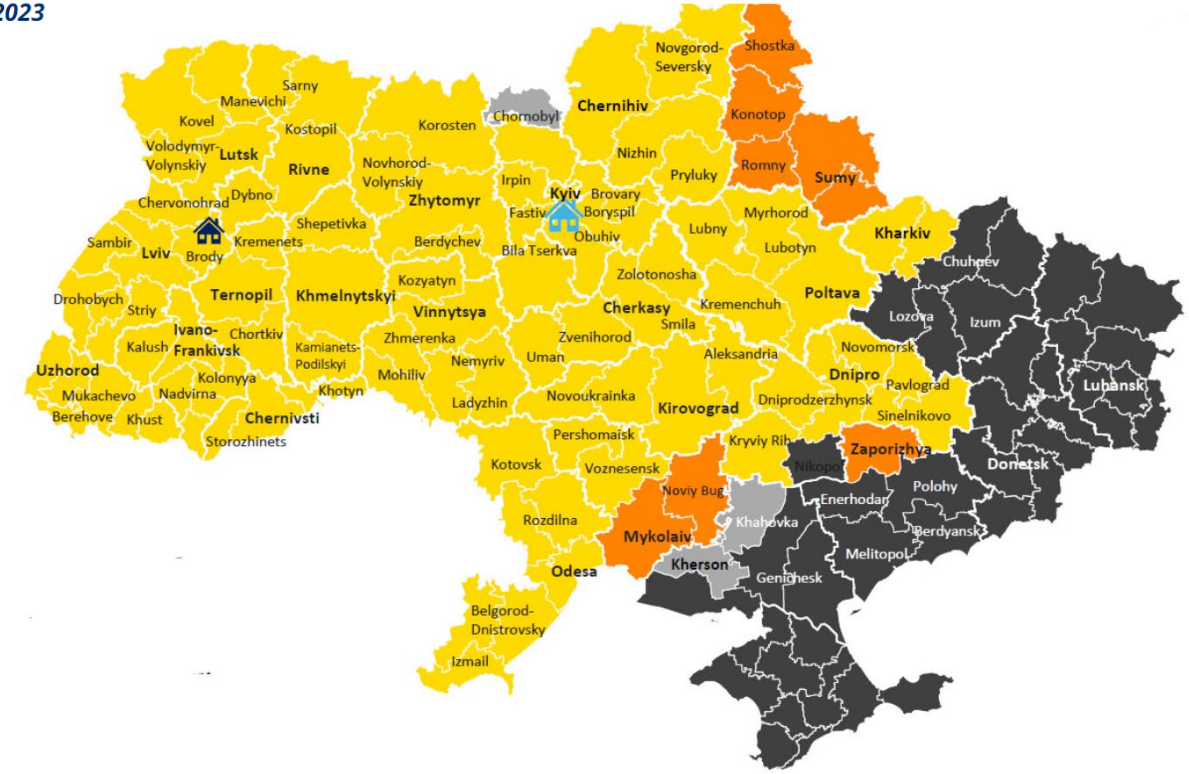
In Ukraine before 01-Jun-2022, rSDV was justified only in specific cases:

- in COVID-19 treatment/prophylaxis clinical trial or
- at the stage of interim or final database locks

Currently, it is allowed to perform rSDV in Ukraine unless specified otherwise in ICF, study protocol, site monitoring plan, SOPs and any other study documents (contracts, delegation of responsibilities etc.).

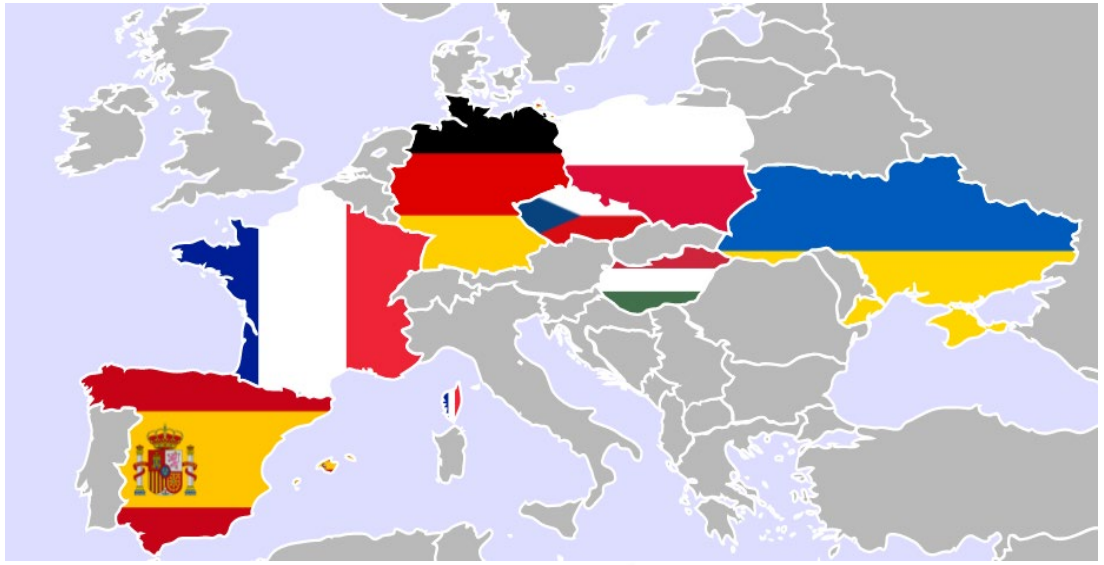
IP supplies by logistics vendor





- Stock accumulated for 2-3 months supplies
- Backup depot open in Western part of Ukraine
- Cross-protocol transfers
- Site-to-site transfer
- Medication delivery to patient home (special cases)
- Constant contact regarding temperature excursions
- From **8 regions** transportation was possible in March 2022 **to 20 regions** in April 2023
- Smart temperature monitoring system pilot at selected sites

Patient transfers



Three scenarios for patients willing to flee from the war

- **Transfer within Ukraine** (another site or another city)
    - Consistent regulatory umbrella
    - Same principles of work with Local Ethics Committees
    - Available ICF
    - Patients' health insurance
- **International transfer** (same study of standard of care in other country)
    - The new regulatory umbrella and Ethics Committees
    - Patient-facing materials preparation and translation
    - Status of the receiving site
    - Availability of medication supplies
    - Insurance
    - Translator to enable communication with the patients
- **Discontinuation of trial access**

2/3 of patients who left abroad returned

Many agencies updated guidelines and issued recommendations specifically for receiving patients from Ukraine.

Short summary

- ✓ Monitoring in place
- ✓ IP and other logistics set
- ✓ Processes working
- ✓ Inspections resumed
- ✓ Vendors working
- ✓ Sponsor’s oversight in place
- ✓ No critical quality issues observed
- ✓ Remote methods implemented
- ✓ New technologies mastered

- ✓ Business continuity in place

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