History

1937: 107 people, many of them children, died as a result of poisoning with an elixir of sulphanilamide containing **diethylene glycol as a solvent**.

1938: Food, Drug and Cosmetic Act - Requirement for collection of **clinical safety data on new drugs** and submission of such data to the FDA prior to approval

1938: Aspirin noted to be a cause of gastric haemorrhage, 39 years after its first use

1960: **Thalidomide Disaster**

1964: UK introduced "**Yellow Card Scheme**"

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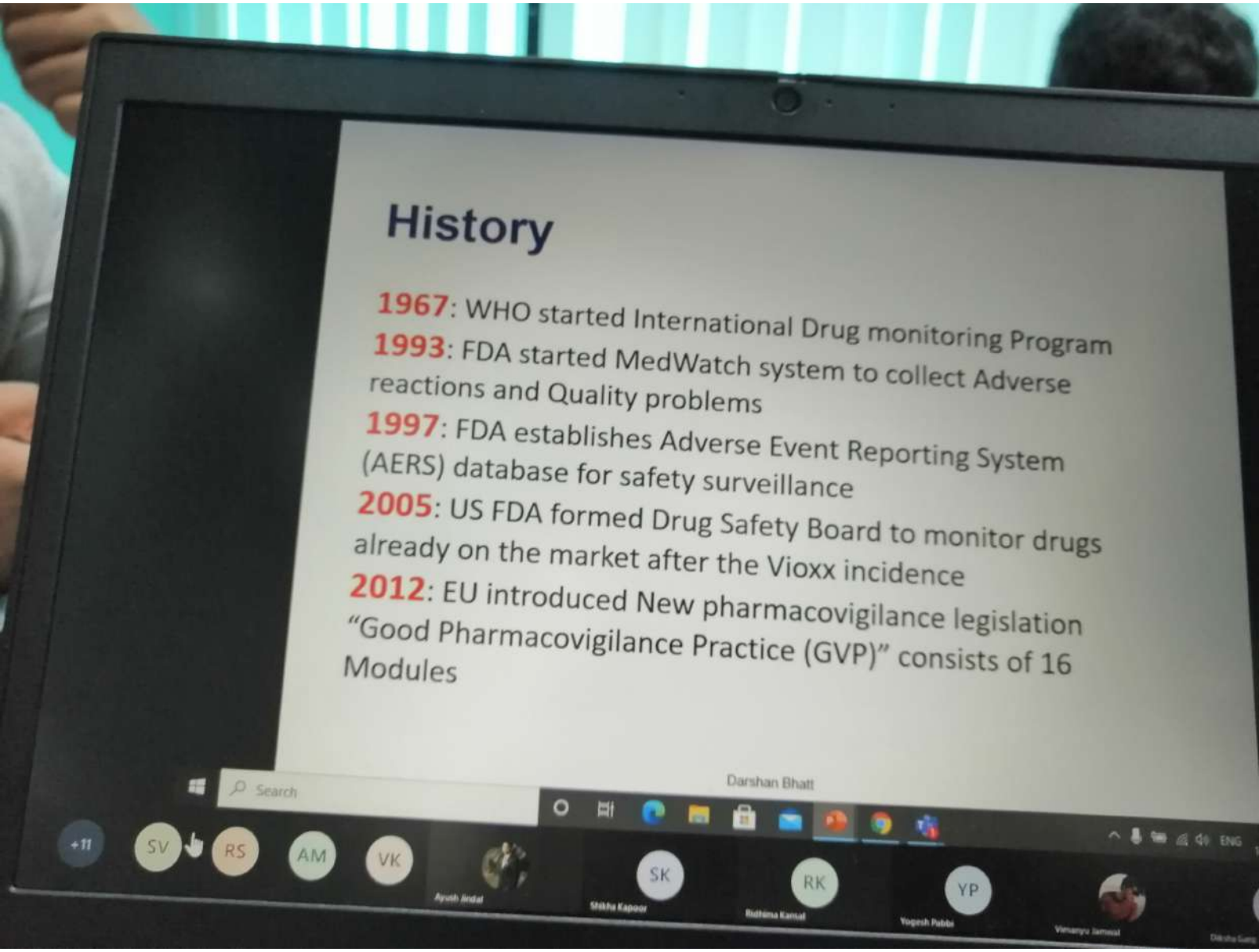
History
1967: WHO started International Drug monitoring Program
1993: FDA started MedWatch system to collect Adverse reactions and Quality problems
1997: FDA establishes Adverse Event Reporting System (AERS) database for safety surveillance
2005: US FDA formed Drug Safety Board to monitor drugs already on the market after the Vioxx incidence
2012: EU introduced New pharmacovigilance legislation "Good Pharmacovigilance Practice (GVP)" consists of 16 Modules
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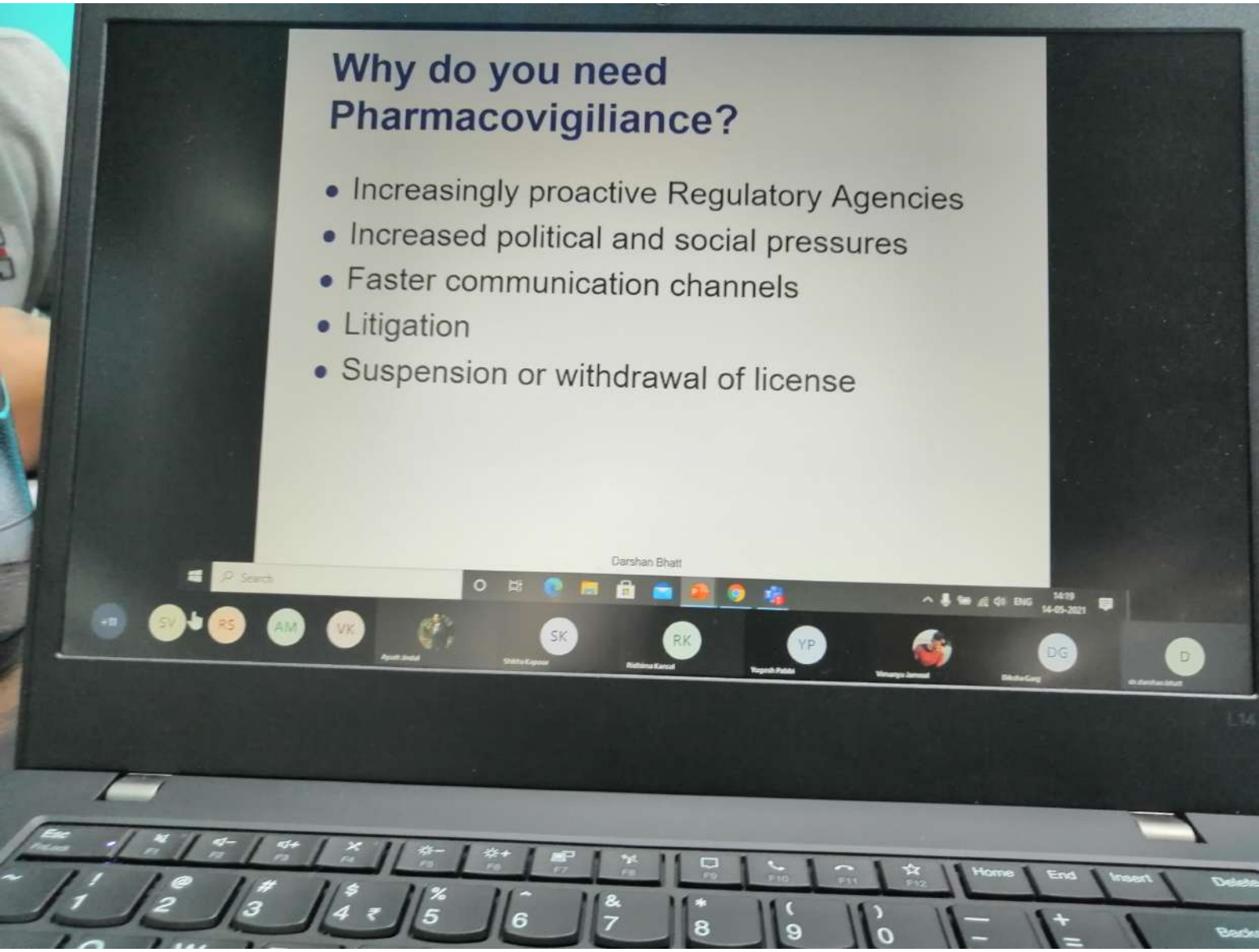
Why do you need Pharmacovigiliance?
Increasingly proactive Regulatory Agencies
Increased political and social pressures
Faster communication channels
Litigation
Suspension or withdrawal of license
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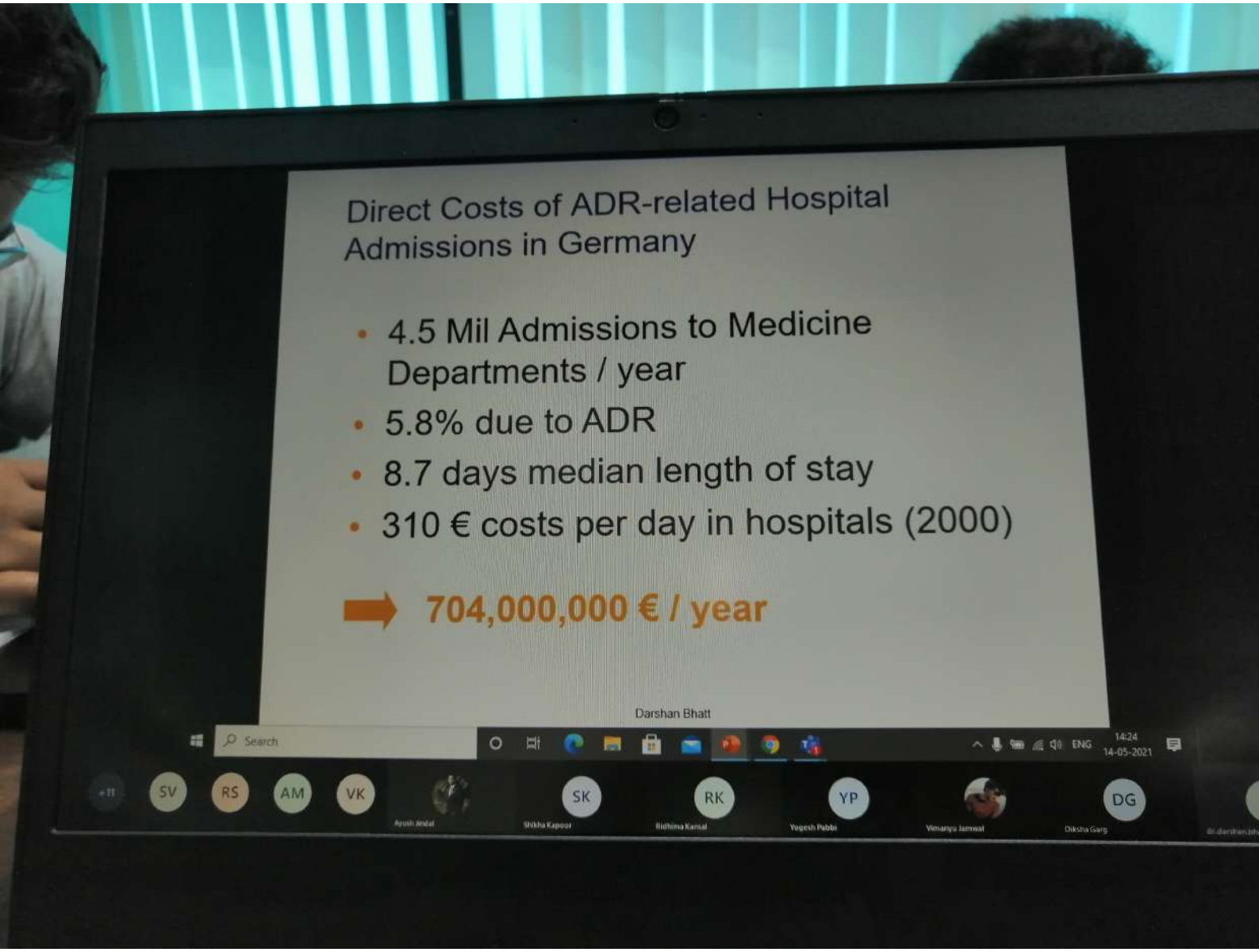
Direct Costs of ADR-related Hospital Admissions in Germany
4.5 Mil Admissions to Medicine Departments / year
5.8% due to ADR
8.7 days median length of stay
310 € costs per day in hospitals (2000)
704,000,000 € / year
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Vimanyu Jamwal
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Diksha Garg

ADR Burden

- ADRs accounted for 4.2% of all ER visits (Yee et al, Ann Pharmacother, 2005)
- ADRs accounted for 2.8% of all ER visits (Malhotra et al, Int J Clin Pharmacol Ther, 2001)
- Of >16000 patients visit to ER in an Italian hospital 2.6% had ADRs and 24% were hospitalised (Zanocchi et al,Recenti Prog Med, 2006)

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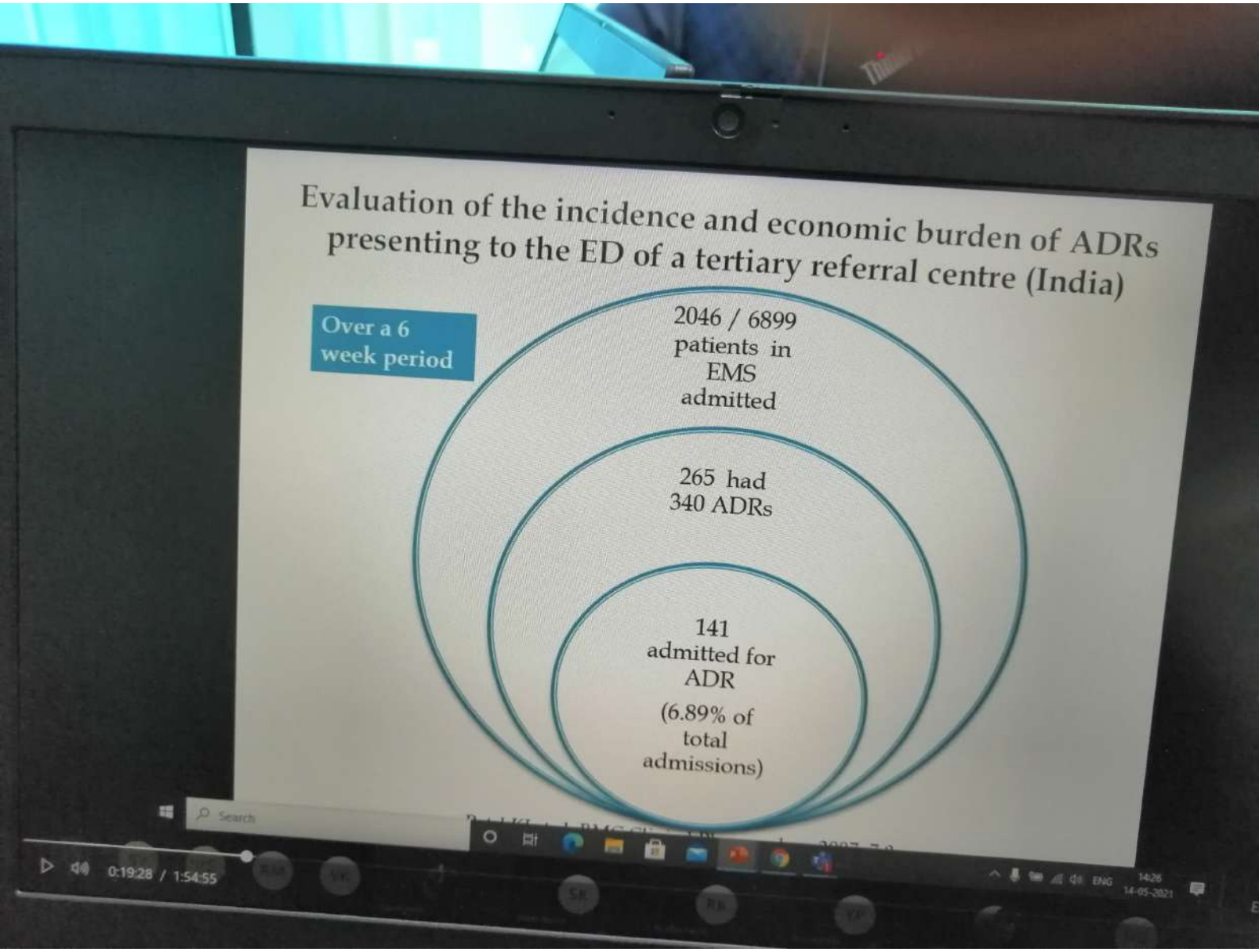
Evaluation of the incidence and economic burden of ADRs presenting to the ED of a tertiary referral centre (India)
Over a 6 week period
2046 / 6899 patients in EMS admitted
265 had 340 ADRs
141 admitted for ADR
(6.89% of total admissions)
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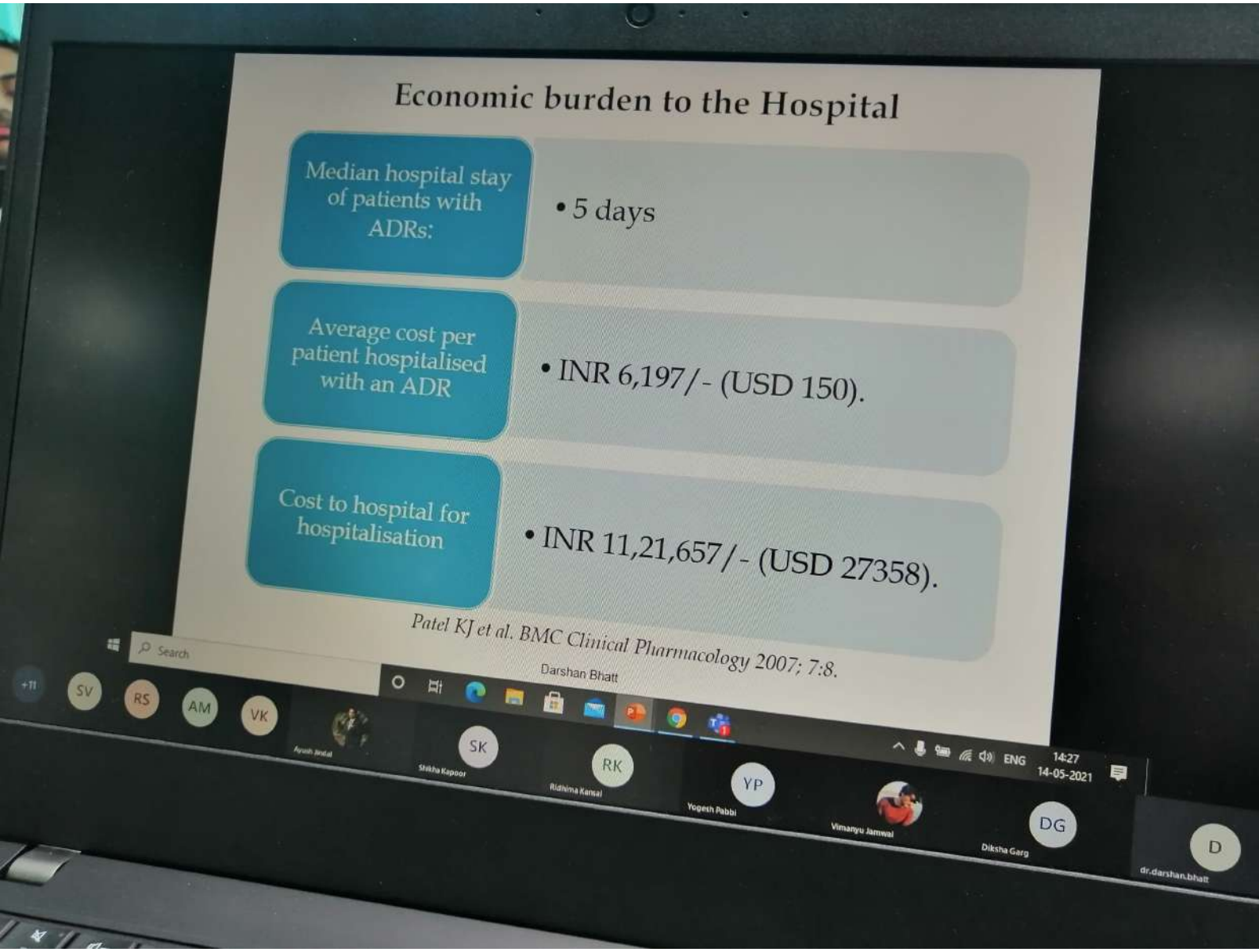
Economic burden to the Hospital
Median hospital stay of patients with ADRs:
• 5 days
Average cost per patient hospitalised with an ADR
• INR 6,197/- (USD 150).
Cost to hospital for hospitalisation
• INR 11,21,657/- (USD 27358).
Patel KJ et al. BMC Clinical Pharmacology 2007; 7:8.
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Ridhima Kansal
Yogesh Pabbi
Vimanyu Jamwal
Diksha Garg
dr.darshan.bhatt

Medicinal Product

A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

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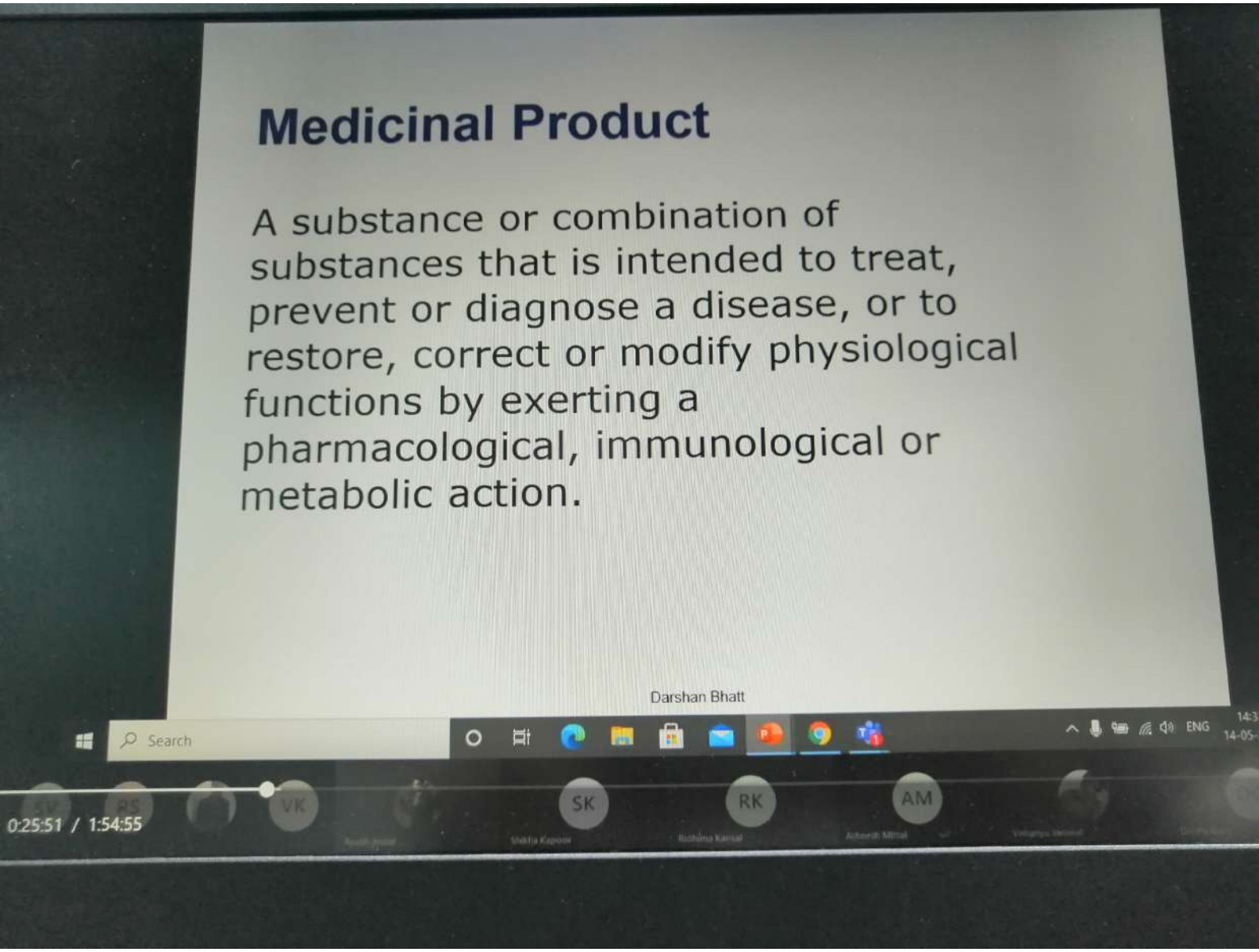

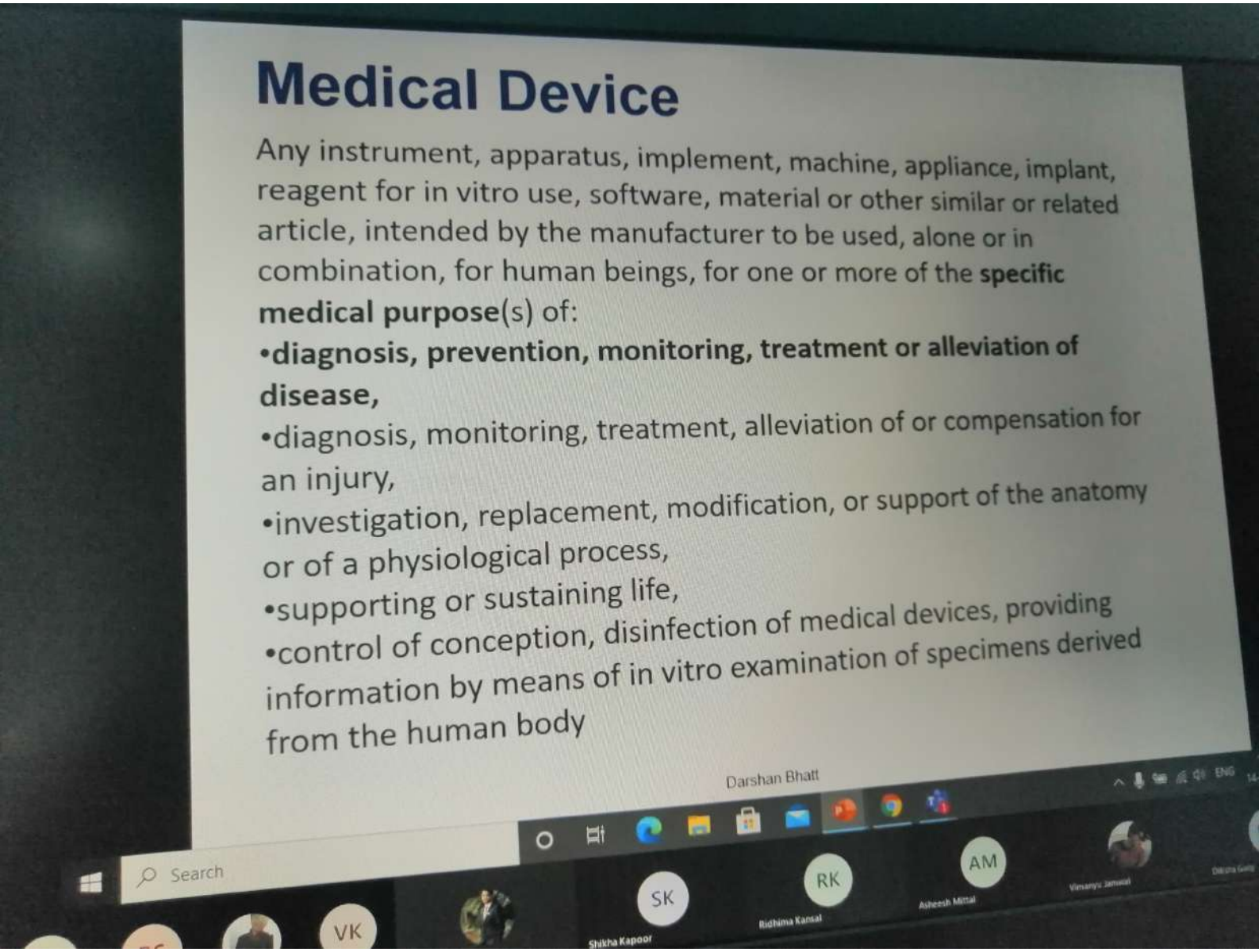
Medical Device
Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:
•diagnosis, prevention, monitoring, treatment or alleviation of disease,
•diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
•investigation, replacement, modification, or support of the anatomy or of a physiological process,
•supporting or sustaining life,
•control of conception, disinfection of medical devices, providing information by means of in vitro examination of specimens derived from the human body
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An Adverse Event is:

"Any undesirable experience occurring in a patient with a pharmaceutical product, whether or not considered related to the medicinal product"

An Adverse (Drug) Reaction is:

"A reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis diagnosis or treatment of disease or the modification of physiological function"

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ADR: New Definition

EU: [DIR 2001/83/EC Art 1(11)]1

'a response to a medicinal product which is noxious and unintended'

Reporting of ADRs is *not limited to adverse effects in normal conditions of use*, but also from :

- uses outside terms of Marketing Authorisation (including misuse and abuse)
- medication error
- overdose
- occupational exposure

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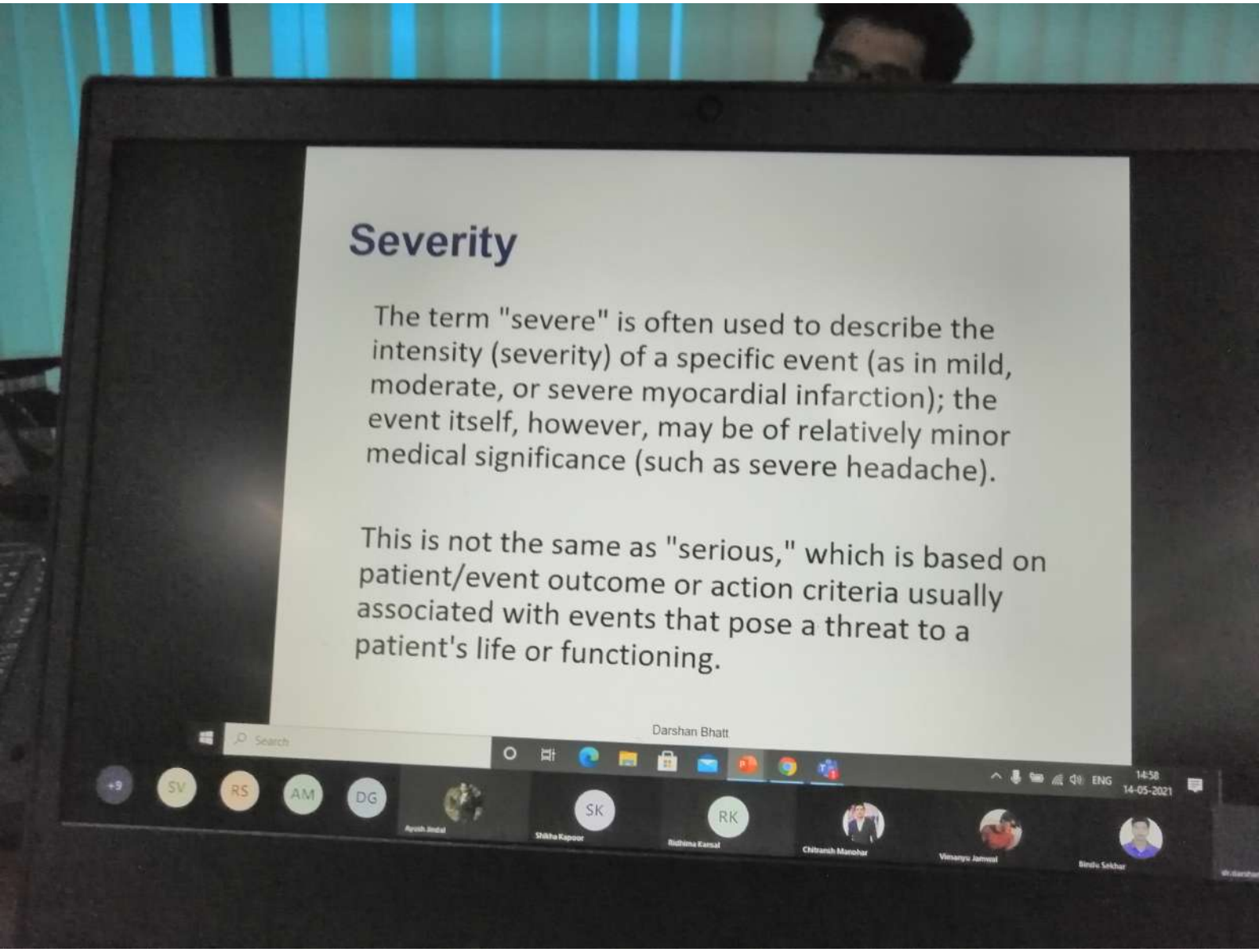
Severity
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.
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Ridhima Kansal
Chitransh Manohar
Vimanyu Jamwal
Bindu Sekhar

Expectedness

An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s).

Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

SUSAR

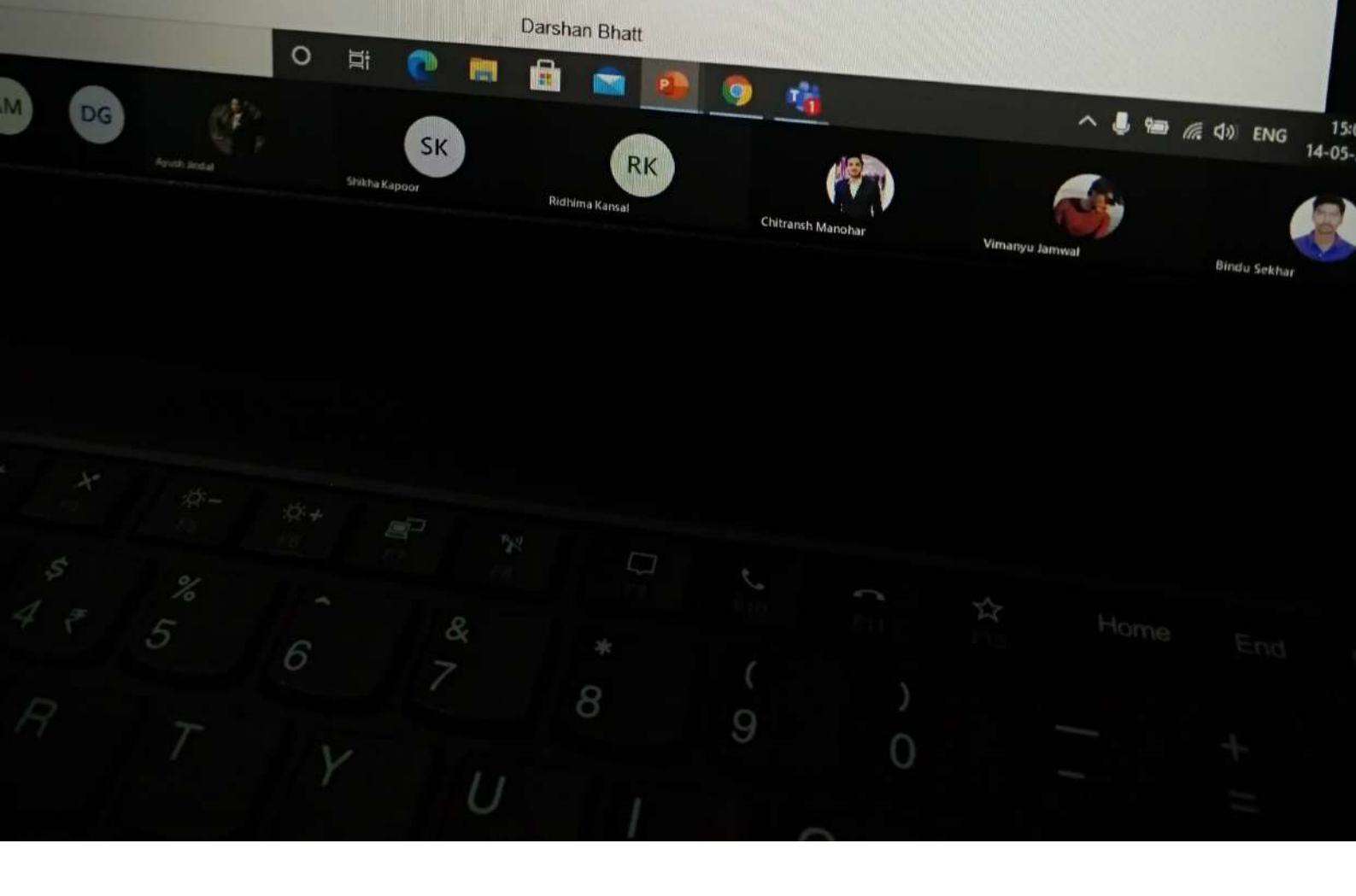
Suspected

Unexpected

Serious

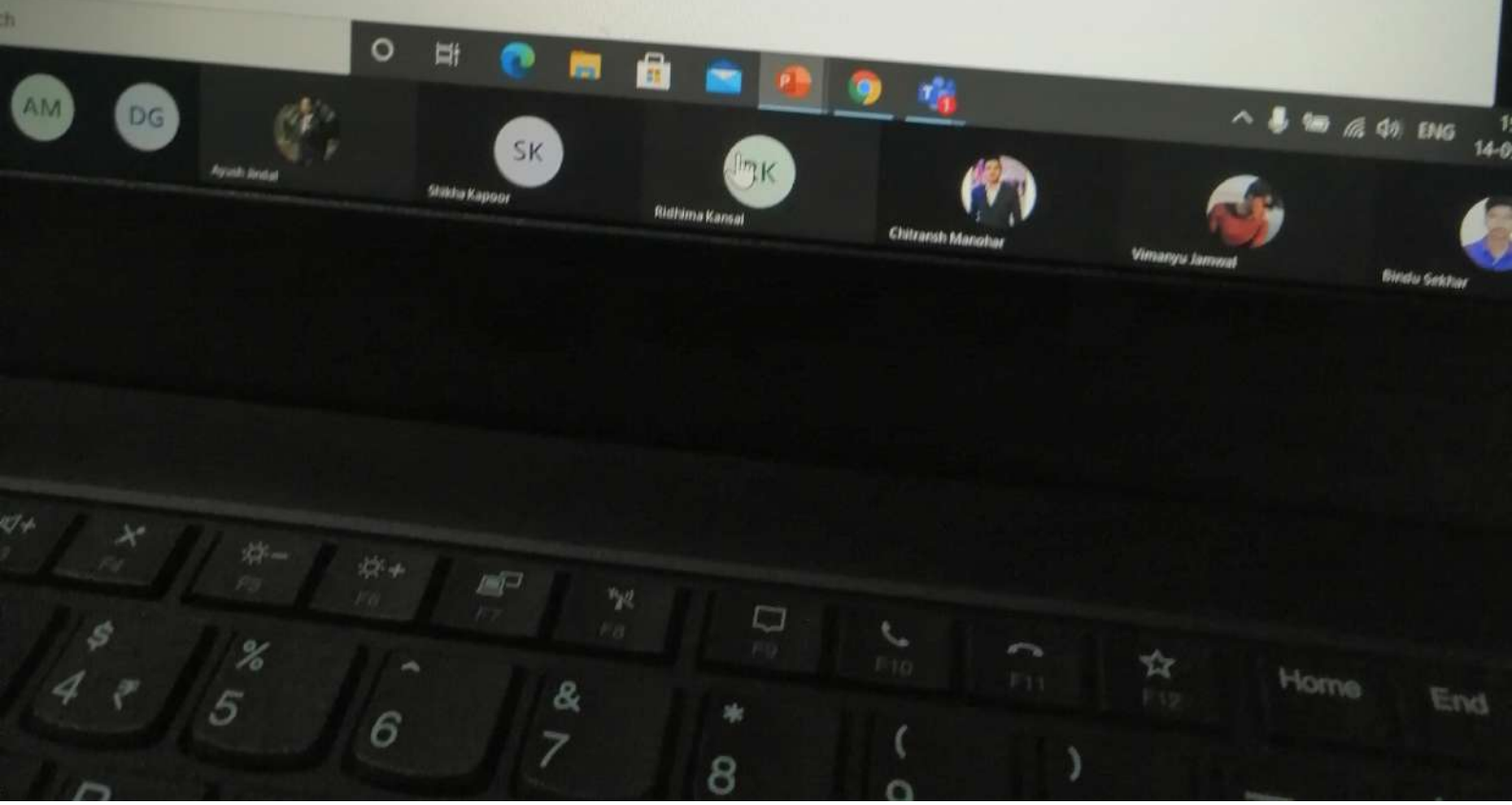
Adverse

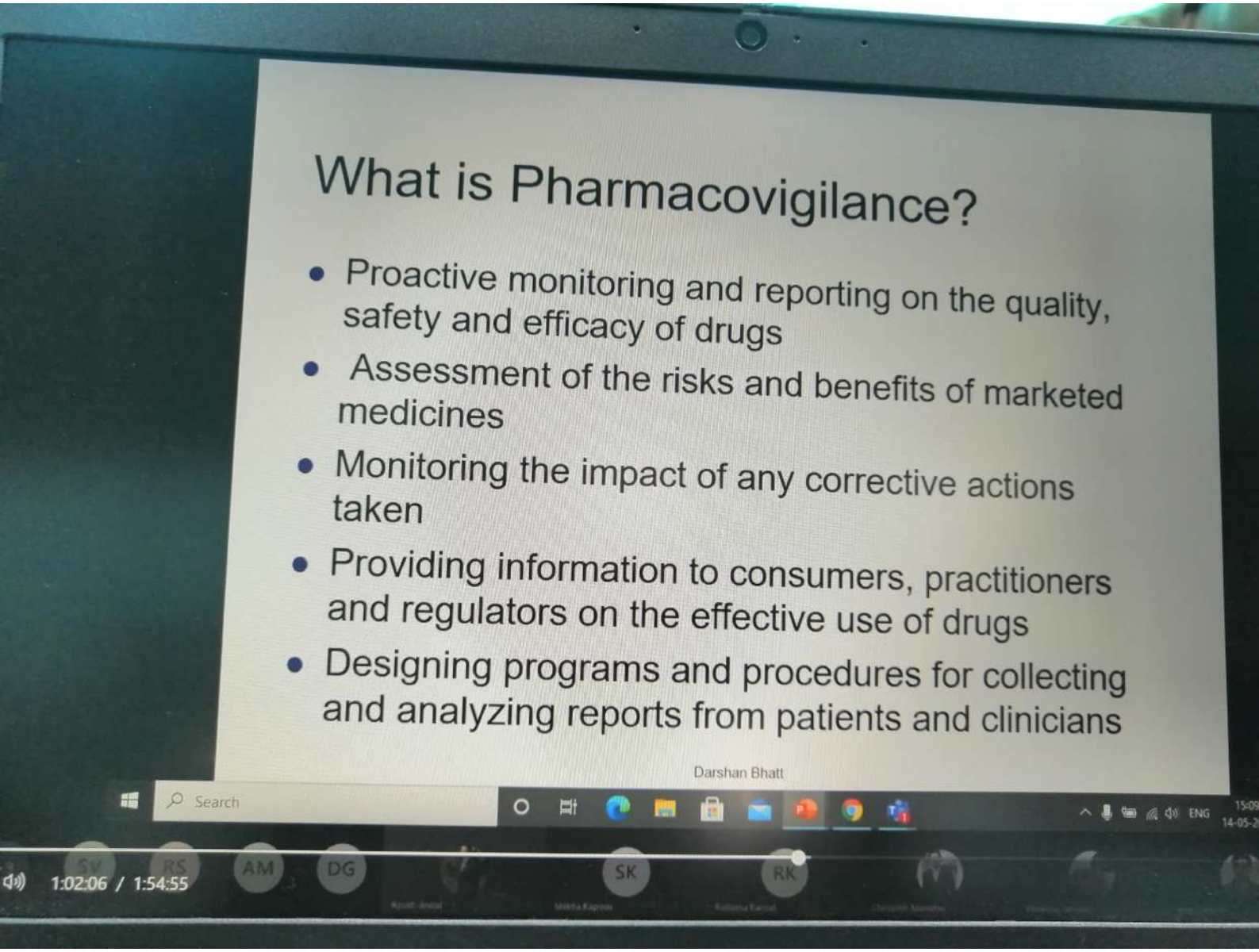
Reaction



Dechallenge & Rechallenge

- Dechallenge – Suspected drug was discontinued as a result of event
- Rechallenge – Suspected drug was re-introduced after previously being discontinued




What is Pharmacovigilance?
Proactive monitoring and reporting on the quality, safety and efficacy of drugs
Assessment of the risks and benefits of marketed medicines
Monitoring the impact of any corrective actions taken
Providing information to consumers, practitioners and regulators on the effective use of drugs
Designing programs and procedures for collecting and analyzing reports from patients and clinicians
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What is pharmacovigilance?

- Safety monitoring and evaluation throughout whole life-cycle of a product
- Encompasses non-clinical, clinical, post-marketing safety data
- Evaluation requires a holistic approach
- Signals detected during development do not necessarily kill the product

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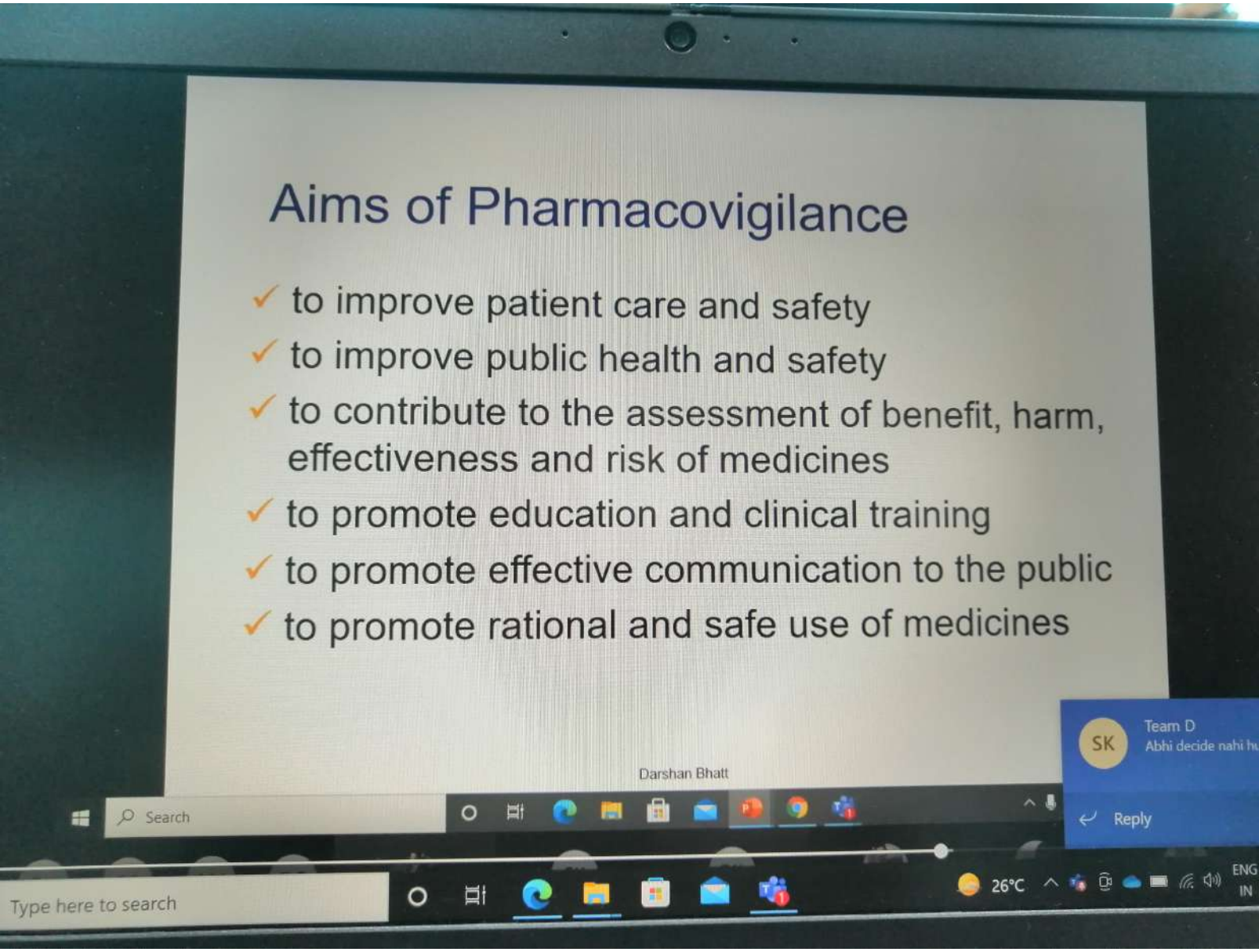
Purpose

- To add value to company's products and safeguard the success of our business by:
- Focusing on the protection of patients who receive company's products
- Delivering high quality product safety information to our customers throughout the product life cycle
- Providing integrated strategic and operational safety expertise to clinical development programmes
- Carrying out active pharmacovigilance with rapid identification and analysis of safety signals to define the safety profile of company's products and facilitate risk management
- Ensuring regulatory compliance


Aims of Pharmacovigilance
to improve patient care and safety
to improve public health and safety
to contribute to the assessment of benefit, harm, effectiveness and risk of medicines
to promote education and clinical training
to promote effective communication to the public
to promote rational and safe use of medicines
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Pharmacovigilance Process

- ✓ collects, records, codes ADEs / ADRs
- ✓ analyses and assesses the reports
- ✓ promotes the safe use of drugs
- ✓ creates appropriate structures and means of communication needed to perform its tasks

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Components of Pharmacovigilance

- *Data Collection*
- *Validation*
- *Entry To Database*
- *Analysis*
- *Signal Generation*
- *Signal Interpretation*
- *Signal Verification: Studies*
- *Reporting*

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Shikha Kapoor

RK

Ridhima Kansal


Chitransh Manohar


Vimanyu Jaiswal

Pre-market Reports

AEs

- High quality information
- High follow up opportunity
- Known denominator
- Complete reporting (hopefully)
- Comparator
- Investigator+ company causality assessment

BUT

- Seriousness at discretion of investigator
- Limited non serious AE information.
- Probably no company causality assessment
- Short exposure
- Exclusion criteria
- Studies not powered to detect rare events

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Post Market Reports

AEs

- Naturalistic setting
- SAEs and AEs
- Company can decide seriousness

BUT

- Under reporting (10%)
- External factors affect
- No denominator
- Incomplete information

Adverse Event Data

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CASE REPORTING TIMELINES

- Fatal, life threatening and keep under review (KUR) cases - 7 days
- Globally expedited – 15 days
- From date of receipt by a Co. to reporting to regulatory authorities world wide
- Clock starts when anyone in a Co. receives the adverse event information

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Reporting of SUSARs

- All SUSARs require expedited reporting (unblinded)
- Includes those associated with:
  - The IMP in the concerned trial
  - The IMP in a trial conducted by the sponsor in a non EU country where the same IMP is being tested in a trial within the EU
  - Spontaneous reports
  - Literature/publications
  - Another Regulatory authority reports
- Includes SUSARs associated with an active comparator

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Reporting of SUSARs

- Concerned Competent Authorities
  - Electronically
  - CIOMS I, include EudraCT number
  - 7/15 day timeframe
- Eudravigilance/EMEA
- Ethics Committees
  - Locally expedited
  - Others may be provided as a quarterly line listing provided any new issues/increased risk are provided within 15 days
- Investigators
- (MAH)
  - Recommended for comparators

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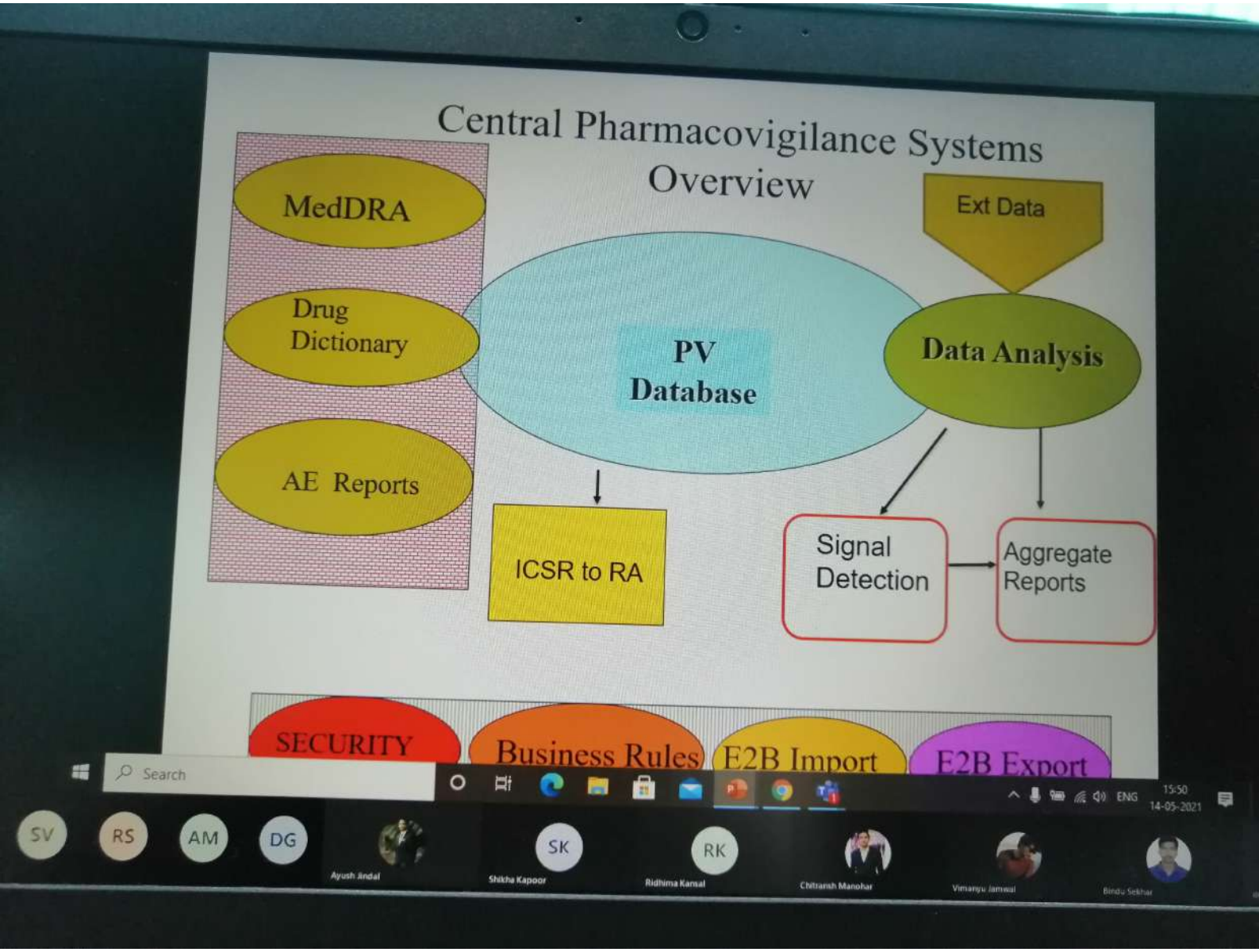
Central Pharmacovigilance Systems Overview
MedDRA
Drug Dictionary
AE Reports
PV Database
Ext Data
Data Analysis
ICSR to RA
Signal Detection
Aggregate Reports
SECURITY
Business Rules
E2B Import
E2B Export
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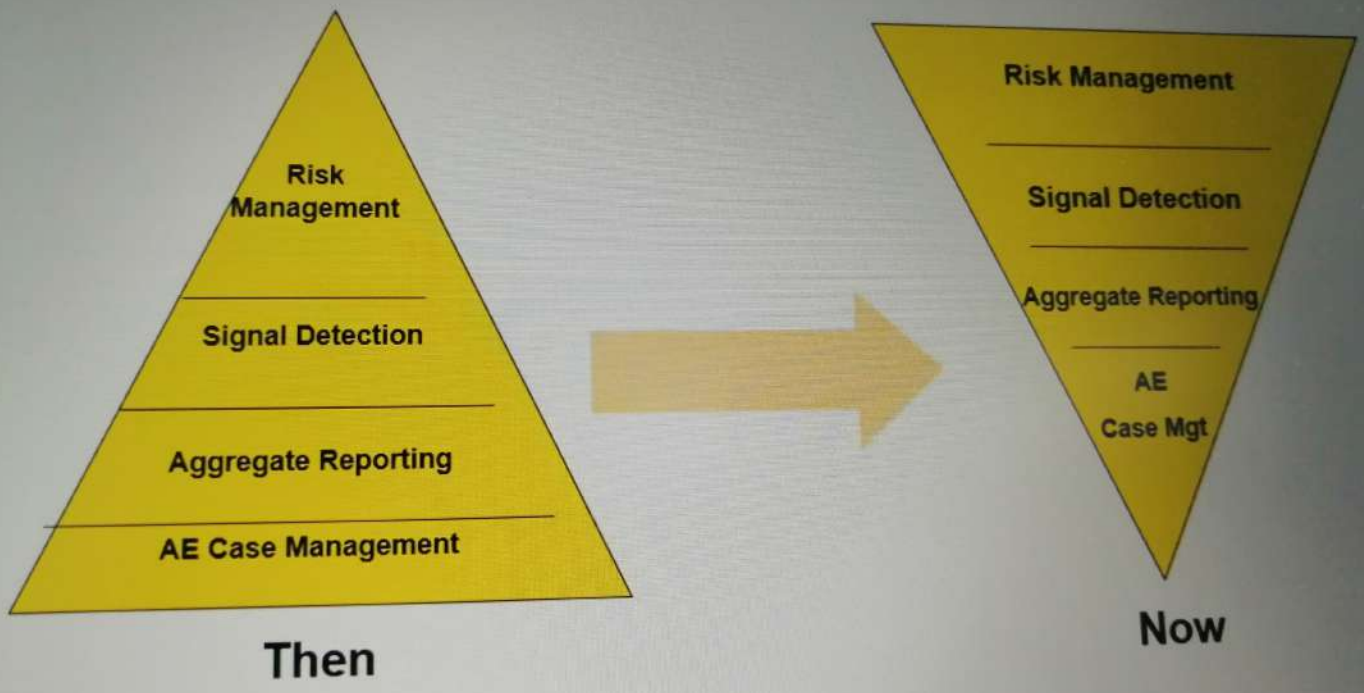
Vimanyu Jamwal
Bindu Sekhar

Paradigm Shift



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Pharmacovigilance...what is this all about?

- **Pharmocovigilance**
  - **Pharmakon** (Greek), "drug" and **vigilare** (Latin), "to keep aware or alert, to keep watch"
  - Ultimate Goal – **Is a product safe to use** – In accordance with labeling with respect to
    - Dose, Patient Age, Gender Medical or concurrent history, Concomitant Medications, Food/Drug Interactions etc.
  - Are the risks associated with the use of the product appropriate to the benefits of the product to the patient?
    - Higher risks are associated with products used to treat cancer versus less life-threatening conditions.

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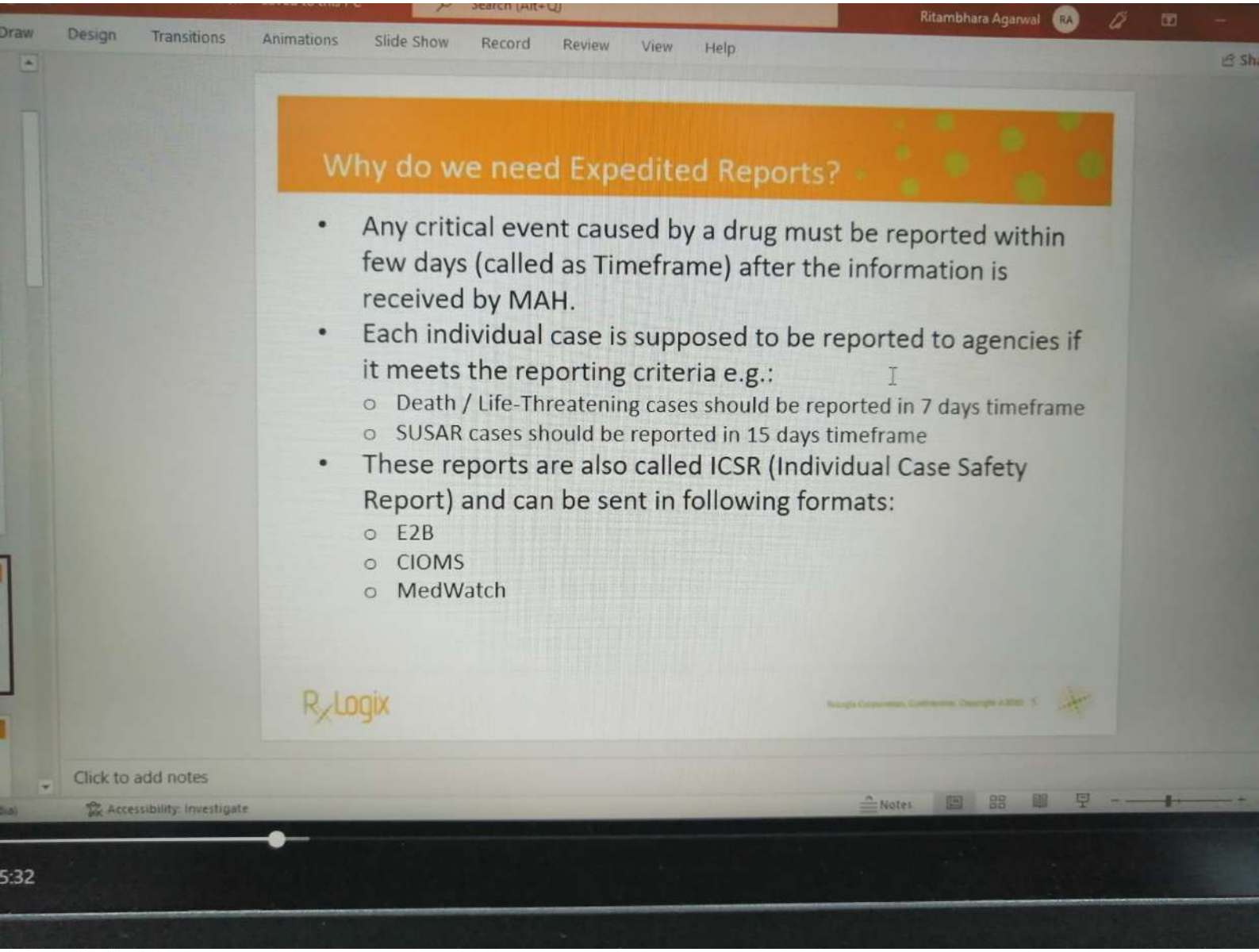
Draw
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Help
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Why do we need Expedited Reports?
Any critical event caused by a drug must be reported within few days (called as Timeframe) after the information is received by MAH.
Each individual case is supposed to be reported to agencies if it meets the reporting criteria e.g.:
Death / Life-Threatening cases should be reported in 7 days timeframe
SUSAR cases should be reported in 15 days timeframe
These reports are also called ICSR (Individual Case Safety Report) and can be sent in following formats:
E2B
CIOMS
MedWatch
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Can you explain some terminologies?

- Datasheet & Listedness
  - Each drug when licensed in a country has to provide a label with list of expected events. These labels are called **Datasheet**.
    - IB (Investigational Brochure) – For investigational drugs
    - USPI (United States Product Insert) – For drugs marketed in US
    - SmPC (Summary of Product Characteristics) – For drugs marketed in EU
    - CCDS (Company Core Datasheet) – Datasheet for global use -
  - Listed AE means it is present in the label and expected to occur.
  - Unlisted AE means it is not present in the label and not expected to occur.

Can you explain some terminologies?

- Causality
  - Causal relationship between drug and AE whether this AE was caused by this drug.
  - Reportable (or Related) causality means AE was caused by the drug. Such events are called ADRs (Adverse Drug Reaction).
  - Non-reportable (or Not Related) causality means AE was not caused by the drug
  - A case has Reporter Causality and Company Causality
  - Conservative Causality refers to the most aggressive out of reporter and company causality i.e.
    - If any causality is reportable, conservative causality is reportable.
    - Only when both are non-reportable, the conservative causality is non-reportable.

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PV terminologies

- **SAR** – Serious Adverse Reaction
- **ADR**- Adverse Drug Reactions
- **SUSAR**- Suspected Unexpected Serous Adverse Reaction
- **Medication error**- Any mistake in the way a medication is taken or administered (prescription, storage, dispensing, preparation, administration…), that has the potential to harm the patient.

PV terminologies

- **Off-label use or Misuse** -Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the marketing authorization. For instance, medicine used:

- For disease that it is not approved to treat
- Through different route or method of administration
- With different dose
- In different group of patients
- They are not medication errors, as they are intentional.

PV terminologies

- Dechallenge – This refers to the stopping of the drug, usually after an adverse event (AE) or at the end of a planned treatment (e.g. a two week course of ampicillin).
- the drug is fully stopped or decreased in dose and the AE may fully disappear or only partially decrease.

- A positive dechallenge – This refers to the AE disappearing after the stopping of the drug. Thus, the AE (which may really be an adverse reaction – AR) of diarrhea disappeared a day after the patient stopped the ampicillin.

- A negative dechallenge – This refers to the AE NOT disappearing after the stopping of the drug. In our example, the diarrhea continued even after the ampicillin was stopped.

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PV terminologies

- **Rechallenge** – This refers to the restarting of the same drug after having stopped it, usually for an AE. Rechallenges may also be complete or partial. Thus the patient may have restarted ampicillin a week later after having stopped it.

•A positive rechallenge – This refers to the AE recurring after restarting the drug. To have this occur, the AE had to have previously disappeared after the dechallenge in order for it to restart.

•A negative rechallenge – This is the case where the AE does not recur after the drug is restarted.Note the confusion here: With a positive dechallenge the AE disappears but with a positive rechallenge the AE comes back. And vice versa

I heard about Product Dictionary...what is it?

- Contains list of company products with below hierarchical details:
  - Product Family
    - Ingredients
    - Datasheets
  - Product
    - Generic Name – usually the concatenation of ingredients
    - Formulation – Tablet, Capsule, Injection etc.
    - Concentration
    - Indication – Medical condition that this product is supposed to cure
  - License
    - Trade Name
    - License Number
    - Authorization Country
    - Datasheet

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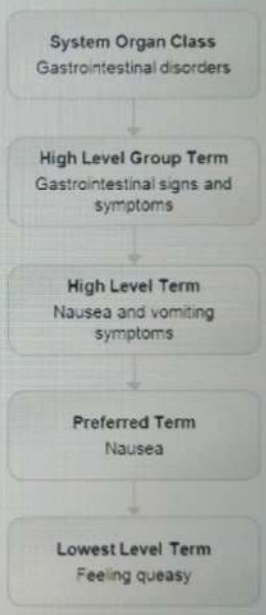
And MedDRA Dictionary...

- **Med**ical **D**ictionary for **R**egulatory **A**ctivities
- It contains list of internationally validated medical terminologies. Below is the hierarchy of this dictionary:



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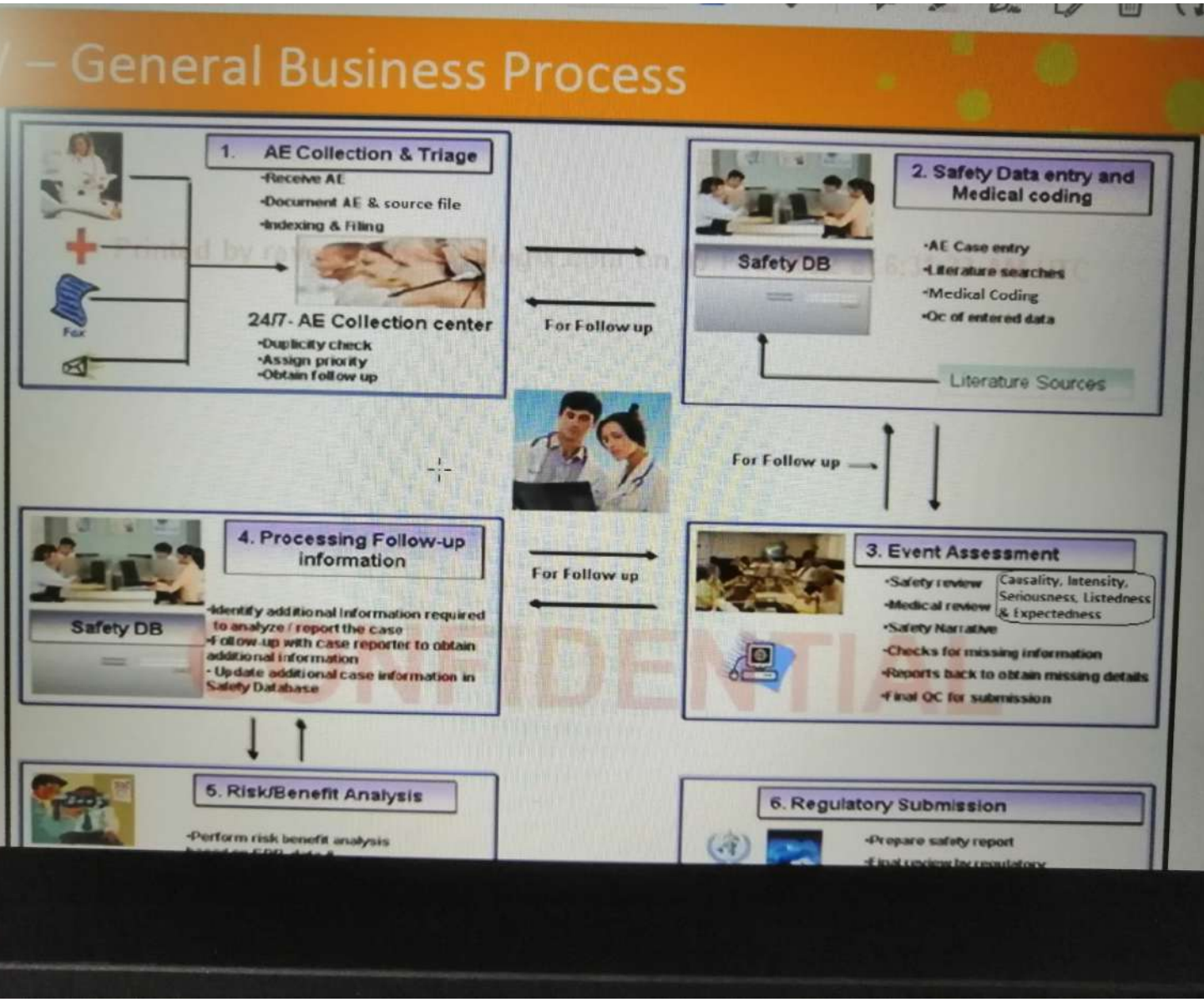
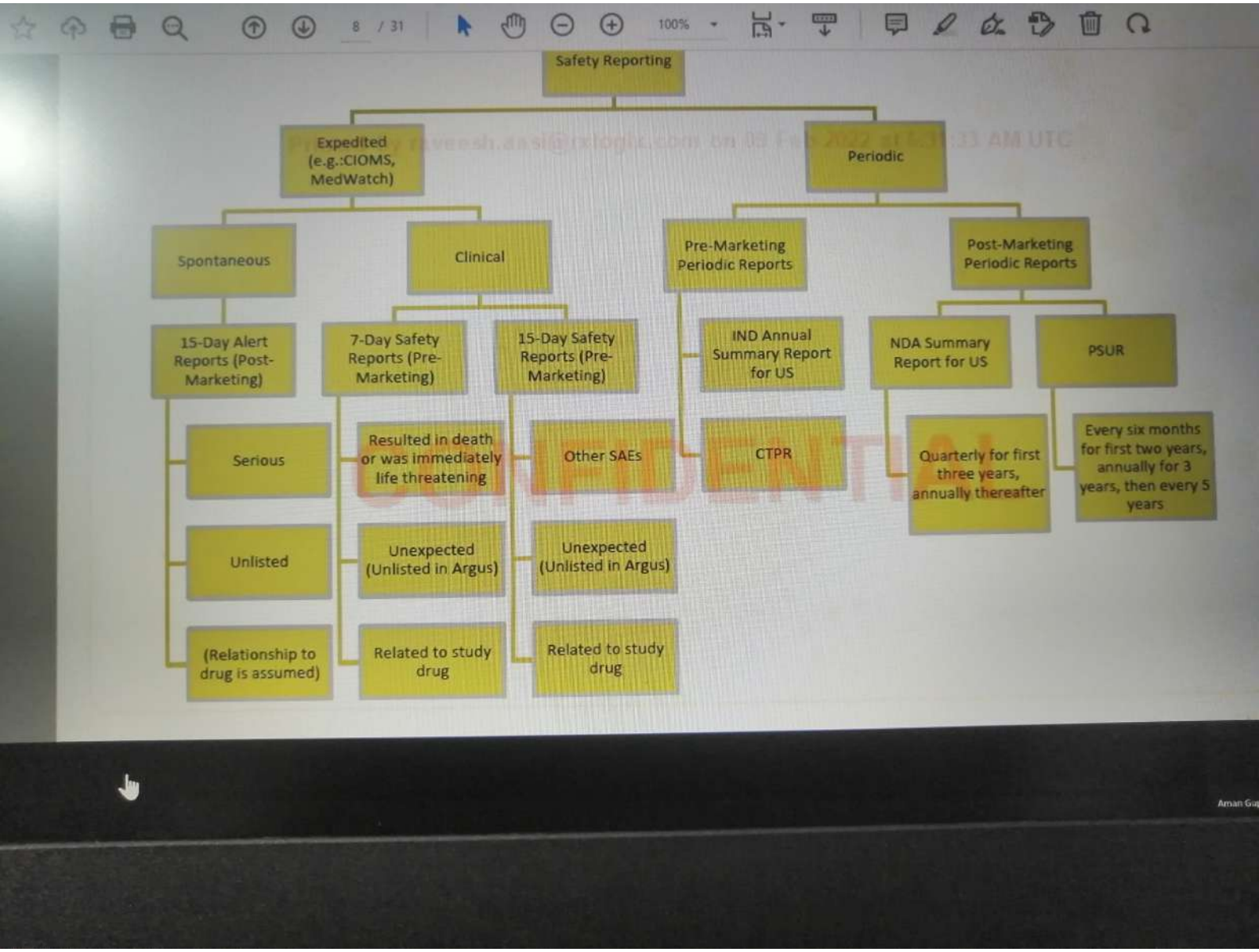
PV – General Business Process




Safety Reporting
Expedited (e.g.:CIOMS, MedWatch)
Periodic
Spontaneous
Clinical
Pre-Marketing Periodic Reports
Post-Marketing Periodic Reports
15-Day Alert Reports (Post-Marketing)
7-Day Safety Reports (Pre-Marketing)
15-Day Safety Reports (Pre-Marketing)
IND Annual Summary Report for US
NDA Summary Report for US
PSUR
Serious
Resulted in death or was immediately life threatening
Other SAEs
CTPR
Quarterly for first three years, annually thereafter
Every six months for first two years, annually for 3 years, then every 5 years
Unlisted
Unexpected (Unlisted in Argus)
Unexpected (Unlisted in Argus)
(Relationship to drug is assumed)
Related to study drug
Related to study drug

Case Processing – Points to consider

- Step 1 – Create case with existing information
- Step 2 - asses Case Priority by initial AE Assessment and License Type
- Step 3 – verify existing information and initiate process of FU (gathering complete information required for analyzing the case)
- Step 4 – Perform Medical review
- Step 5 – Initiate Expedited reporting based on regulatory obligations
- Step 6 – Complete Case processing (data gathering, FU completion and Expedited reporting completion) and Archive it
- Step 7 – Signal Detection

Event Expected	Related
Event Origin	E
	Local

Workflow	Case Classification
Data Entry	-Case details - **Pregnancy Details**
Quality Control	- Pregnancy Details - Essential case fields (Patient, Product, Event and Reporter fields for reporter completion and signal detection)
Medical Review	-Product and Event Assessment - Coding and Narrative - FU consolidation and request * (specifically for Case seriousness post birth)
Reporting	- No Expedited report

RxLogix

arch

ICSR CASE PROCESSING EXERCISE- Spontaneous- SUSAR- Death

Event description	Death
Event Intensity	SEVERE
Event Causality	RELATED
Event Expected	UE
Event Origin	Local

Workflow	Case Specifications
Data Entry	- Case details **- Death and Autopsy details**
Quality Control	- Death and Autopsy details - Essential case fields (Patient, Product, Event and Reporter fields for reporter completion and signal detection)
Medical Review	-Product and Event Assessment - Coding and Narrative - FU consolidation and request
Reporting	- 15 Day Expedited report

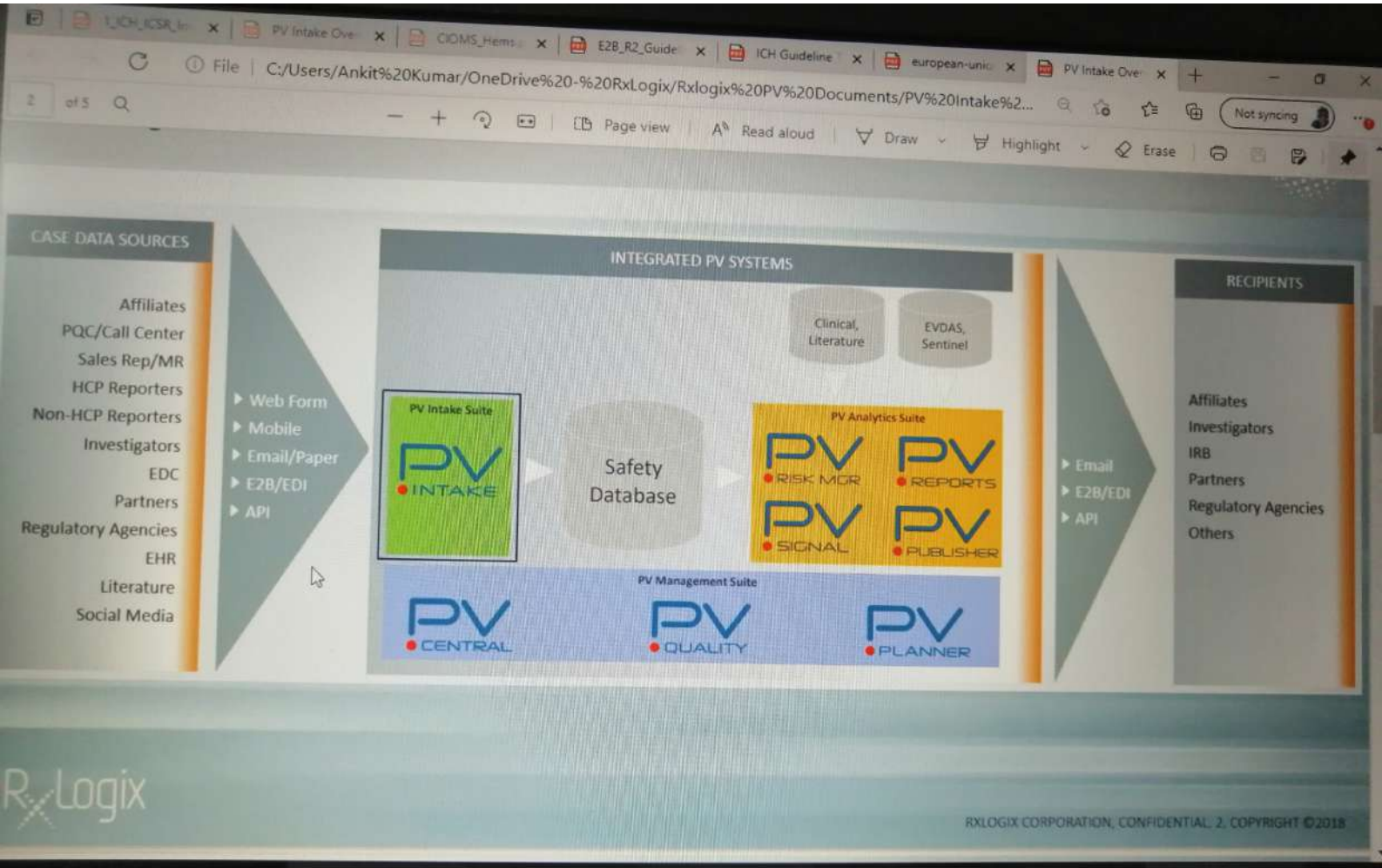
ICSR CASE PROCESSING EXERCISE- Clinical- SUSAR- Death

Event description	death
Event Intensity	Severe
Event Causality	Related
Event Expected	UE
Event Origin	Foreign

Workflow	Case Classification
Data Entry	- Case details **- Death and Autopsy details**
Quality Control	- Death and Autopsy details - Essential case fields (Patient, Product, Event and Reporter fields for reporter completion and signal detection)
Medical Review	- *Unblinding of study product* -Product and Event Assessment - Coding and Narrative - FU consolidation and request
Reporting	- 7 Day Expedited report

Periodic and Expedited Reports

	* Product specific	* Region Specific
Primary aim	-Product Profiling - Product profiling summary for a specified period - Line listings	- Event profiling for regulatory compliance
Expectedness	- Listedness	- Labeledness
Timeline	-2 months to 5 years -E.g. : ICH PSUR 0 to 2 years – Every quarter 2 to 5 years – Every year > 5 years - Every 5 years	7 day or 15 day
Types	- Clinical - CTPR and IND (for USA) - Spont – PSUR and NDA (for USA)	Region specific forms E.g.: MedWatch, MHRA, Spanish
Categories	- by therapeutic area -Sub category by ingredient	-By product type – drugs, vaccine, devices



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