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MÉDECINE SORBONNE UNIVERSITÉ

Challenges associated with the pre-approval of clinical study protocols for pandemic preparedness

The clinician perspective

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Declaration of interests – past 36 months (associated with pandemic preparedness)

- Advisory boards : Moderna, Atea, Shionogi

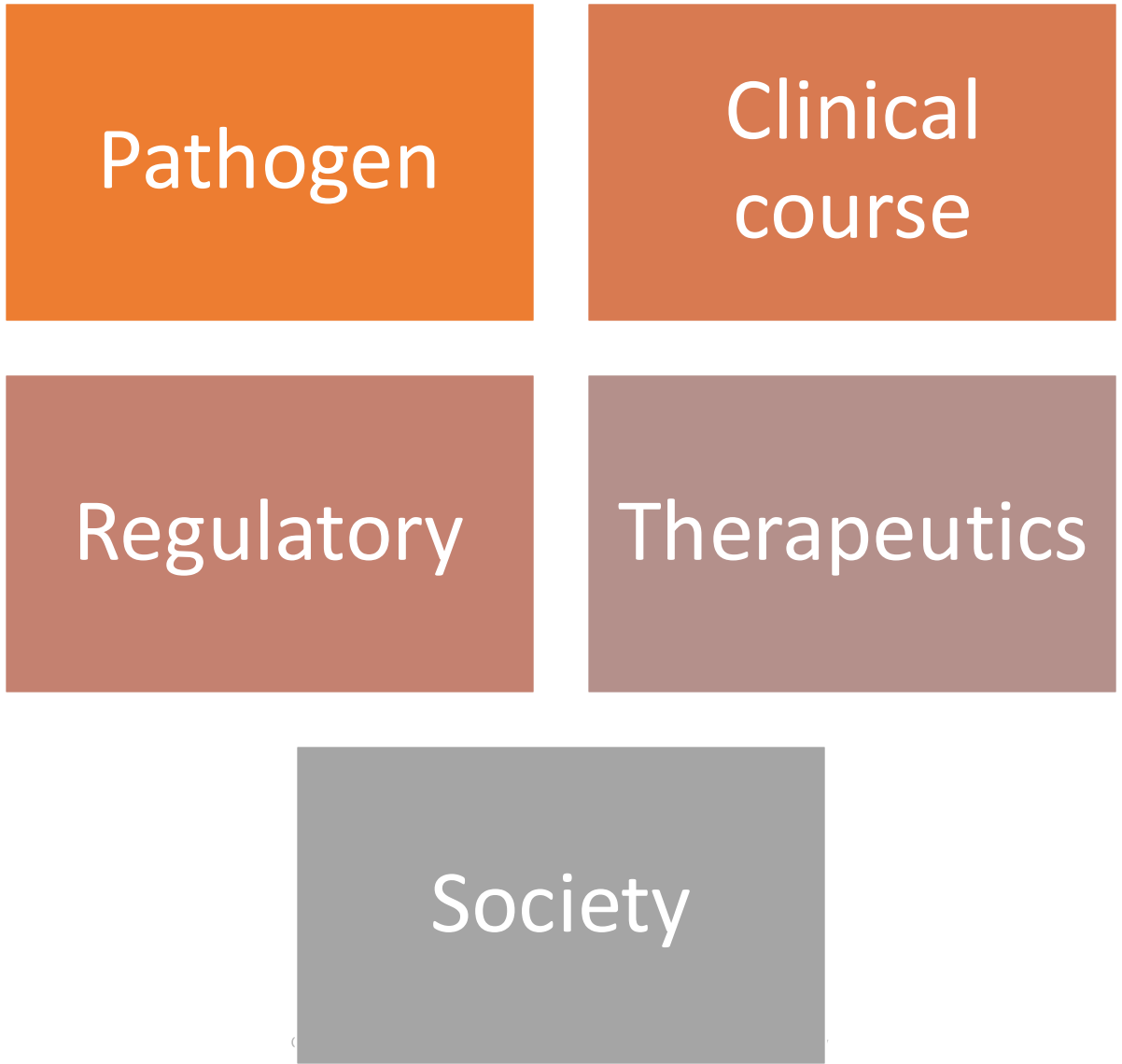
Pandemic = moving environment with a lot of constraints that put pressure on all components of society,

and implementing research during a pandemic means facing that pressure

and trying to find appropriate measures that will allow reaching the objectives of the research initiative

All that applies to designing study protocoles for clinical research

Known & unknown challenges



The pathogen

- Totally unknown pathogen (SARS-CoV2)
- Known pathogen but rare and no formal research prior 1st epidemic (Ebola)
- Known pathogen but rapid mutations leading to treatment and prevention failures (Influenza)

WHO Pathogen X conference

The annual WHO Pathogen X conference was held on August 29-30 in Geneva, Switzerland. Daniel Skyle reports.

REVIEW 463

Updated WHO list of emerging pathogens for a potential future pandemic: Implications for public health and global preparedness

➔ Pathogen poorly characterized keeping clinicians and drug developers in the fog during the 1st weeks/months

The clinical course

- Unknown symptomes and clinical course + no predictive markers of severe evolution of disease

- Multiple consequences :
  - How to define patients at highest risk of severe disease and mortality (priority target for drugs in the early course of an epidemic)?
  - How to choose relevant clinical endpoints except for mortality ?
  - How to accomodate endpoints and interventions in a rapidly evolving field of knowledge, and not appear outdated even before the protocole is implemented?

The regulatory environment

- Logarithmic scale of deaths in an epidemic within days and weeks... Whereas getting a protocole approved by regulatory bodies takes months

➢ *Can regulatory bodies be agile and responsive AND protective of science integrity and participants safety at the same time ?*

- Pre-approved protocols utility may be undermined by requirements for amendments from the authorities

- Evolving standards of care alongside increase in new evidence

➢ *potentially rendering a trial arm obsolete or requiring (multiple) protocol amendments.*

- Emerging evidence from other trials leading to discussions around discontinuation of other trials (ex. Mpox trials)

The therapeutics

- How to identify specific compounds in a record time ?

➔Necessity of getting data on efficacy of repurposed drugs on a range of pathogens before an epidemic emerges

- Lots of in vitro data most of the time but lack of proper testing for efficacy in phase 2 at least*

- Real life experience: pre-approved protocols may rely on drugs or testing devices or components that are not available during a pandemic (as experienced in Belgium with tocilizumab or in France with PCR, swabs, etc.)

* « our old friend hydroxychloroquine which will pop up EVERY time there is pH-dependant steps in viral replication! » - S. Baghani

The society

« ***Clinician hesitancy:*** Physicians may hesitate to enroll patients in protocols that seem inflexible or detached from the clinical realities of the specific outbreak… or because they think there is a "magic bullet" available outside of the clinical trial you propose. »

« Patient hesitancy: Patients may also have heard that a certain treatment works… and you are not offering it in your clinical trial… or they only have 50% chance (or less) of getting it…. while maybe some clinicians are giving it to everyone (without being enrolled in a trial) »

- Maya Hites -

The hard job of integrating equipoise in your thoughts when you are not a trial specialist

Thanks to the great PROACT EU-Response team

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