EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Debrief:
EMA workshop on generating clinical evidence for treatment and prevention options for Long-COVID

PCWP/HCPWP meeting 28 February 2024

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Workshop

- Workshop was **conducted** as a fully virtual event on the **17 Nov 2023**
- **Well attended** by **multiple stakeholders** to address:
  - **Methodology challenges** of **designing clinical studies** for generating robust clinical evidence
  - **Complexity** of the **pathophysiological mechanisms** and **clinical syndromes** associated with Long-COVID that **impacts** the **evaluation** of possible **therapeutic or preventive strategies** in clinical trials

Objectives

- Foster the future identification of optimal **clinical study designs** and **outcome measures** to **reliably assess efficacy** for the **multiple clinical syndromes** of Long-COVID that can generate **robust and reliable efficacy** data needed for regulatory approval
- **Facilitate** future **designing and approval** of clinical studies for treatment and prevention options for Long-COVID

Panel discussion and open discussion

- Several **important topics** were covered
  - The **needs of patients** and **special populations** like paediatric and immunosuppressed patients
  - The role of any available **animal models** for Long-COVID
  - The potential **study design**
  - The advantages and disadvantages of patient-reported outcomes **(PROs) as primary efficacy outcome**
  - The **use of biomarkers** for more **targeted investigations** or to **enrich** the patient population

Key outcomes -1

- Patients are **suffering tremendously** due to some of the **key chronic debilitating symptoms**, and the **associated economic** and **social consequences**.
- Initiate clinical studies **as soon as possible**, to give patients a **chance to access medicines** under investigation in the **secured environment** of a clinical study
- **Well-designed, double-blinded randomised** clinical studies are **essential** to ensure generation of robust and reliable clinical evidence
- Based on the lessons learned from the SARS-COV-2 pandemic **underpowered** or **duplicated studies** with **insufficient clinical study design** should be **avoided**
- Need to **increase collaborative effort** to **facilitate and initiate** coordination of **platforms studies** in the EU, to **better coordinate EU cohorts**, and to **establish EU patients registries**, also for paediatric and immunocompromised patients

Key outcomes -2

- **Real-world evidence → helpful** to gather an **increased understanding** of the disease including its natural history

BUT:

- **Challenge** of **different definitions and categorisation** used across studies and public health institutions
- Important to **strengthen** the **coordination of EU cohorts**, to reach a **common methodology**, an **agreement of definitions** and to **use the huge biobanking**
- Consensus on an **agreed operational case definition** of Long-COVID and/or an applicable diagnostic **ICD-10 definition** for diagnosis across Europe

→ Ensure **proper diagnosis and consistency** of the patient population **across studies** and **cohorts**

Paediatrics

- **Adolescents** should be **included** in **adult clinical trials**
- **Conducting** clinical studies in **younger paediatric** patients is very **challenging**:
  - **Overall prevalence** of Long-COVID is **lower than in adults**
  - **Low test frequency** for acute infection and the consequent **difficulties in identifying patients**
  - Considerably **different Long-COVID clinical phenotypes** compared to adults
  - **Limited applicability** of **patient reported outcomes**
  - **Lack** of established diagnostic **criteria and biomarkers**
- Establishing **paediatric registries**

→ **Most valuable option for paediatrics** to gather information on the disease and treatment outcomes in this population

Animal models

- **Role of animal models** for Long-COVID to identify treatments to be tested in clinical trials is **uncertain**
- **Increasing evidence** that the **hamster SARS-CoV-2 infection model** could be of value for agents aimed at controlling viral replication

  BUT

  → **Validation** and **long-term data** are **missing**

  → Further explore their relevance to human Long-COVID
- Initiation of randomised clinical studies should in principle **not be postponed** unless there are **clearly identified risks**

Clinical study design consideration

- First step an **agreed operational case definition of Long-COVID** and/or **ICD-10 definition** for diagnosis across Europe

  → Ensure **proper diagnosis and consistency** of the **patient population** across clinical trials and cohorts.

- **Treatment** of Long-COVID should be **prioritised** over prevention
- Patients with the **most severe clinical manifestations,** e.g., exercise intolerance or chronic fatigue, should be **addressed first**
- Initial focus on **clinical phenotypes** or **symptom clusters** (I,e, ME/CFS (Myalgic Encephalomyelitis / Chronic Fatigue Syndrome) **irrespective of origin**

  → Might be **challenging**, considering the **overlap of symptoms** from **different clusters**

Primary endpoint

Patient Reported Outcomes (PROs)

- Patient reported outcomes (PROs) are presently considered to be the **best option**
- Use of already well-known, **disease specific PROs preferred**, which should be **adapted and validated for Long-COVID**.
- Consider **learnings and outcomes** from PRO from other initiatives like RECOVER

Biomarker

- In proof-of-concept studies, to **confirm** the **mechanism of action** and **biological plausibility**
- **Not** yet **sufficient clinical evidence** to **support** the use of biomarkers as **surrogates of efficacy**
- Useful to **enrich the patient population** to select those who will benefit most from treatment

Conclusion

- Patients are **in need of treatment now** and investigations on potentially effective treatments should **not be delayed**.
- **Off –label use** of medicines that are not tested in scientifically sound clinical trials **need to be avoided**.
- **Increased collaborative effort is needed** to facilitate and initiate coordination of platform studies in the EU
- **More funds** to **support the conduct** of Long-COVID clinical trials in the EU should be made available
- Find a way to **synergise and capitalise** on the work done by the NIH Recovery initiative
- Summary report and a publication are **currently drafted**
- A **further meeting** will be organised in **mid/end 2024** to take stock of the advancements gained and to check the state of play

Any questions?

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