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

1. Debrief: EMA workshop on generating clinical evidence 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

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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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