It would be more useful to find out how to make our genome permanently worry-free rather than looking for palliative solutions.

Some ethics specialists believe that they are alone on what they believe to be the right path to progress! They want the slow road that will leave billions of deaths behind because of the lack of preventive/curative care that genome modifications would have allowed.

This vision exasperates me because patients need concrete solutions, not moral bullshit.

Arnaud D. Longevity activist, private email in November 2020.

Theme of the month: Clinical Testing and Longevity

Clinical Trials

Clinical trials are an essential phase in the development of new drugs. Halfway between research in the laboratory, on cultured cells or animals (rodents, monkeys...), and patient care, this long process takes place in several phases and ensures that the benefits outweigh any risks. It is an indispensable element in the elaboration of big data for health and longevity.

In particular, clinical trials make it possible to determine the populations for whom the drug is most effective and the optimal conditions of use (route of administration, concentration, dosage, etc.). There are three phases in these clinical trials, necessary before the molecule can be authorized for sale as a drug; plus a fourth phase after the product is marketed.

Phase 1, evaluation of the toxicity of the molecule

A Phase 1 clinical trial is the very first use of a new molecule in humans. It may be remunerated. The molecule is tested over a short period of time, from a few days to a few months and on a small number of people, no more than a few dozen.

The objective of the phase 1 trial is to carry out a short-term assessment of the safety of the product's use, i.e. its possible toxicity, its short-term evolution in the body and an initial pharmacokinetic profile.

In France, the National Agency for the Safety of Medicines (ANSM) states that in this type of first administration trial, "the first dose of the new active substance administered must not cause any detectable short-term toxic effects". According to Leem (French association of drug companies), 30% of products tested fail to pass this first phase.

Phase 2, efficacy and optimal dosage studied

Once toxicity has been studied, it is the efficacy of the product that is evaluated in phase 2 trials. This type of trial is carried out on small homogeneous groups of 10 to 40 patients with the targeted disease, over a period ranging from a few months to 2 years. The aim is to determine the most appropriate dosage, the smallest effective dose for a given pathology, and to optimize the pharmaceutical form of the product. Only one third of products tested would pass Phase 1 and 2 trials.

Phase 3, the study of the benefit/risk ratio of the drug candidate

This time, the drug candidate is tested on a large sample of patients (at least several hundred), often in international studies. This involves comparing the drug in development to a placebo (a drug with no therapeutic effect) or to another proven drug. Ideally, this phase should be carried out with randomly selected groups. The objective is to prove efficacy and to evaluate the efficacy/tolerance and benefit/risk ratios of the molecule. This step should also allow the demonstration of possible interactions with any other simultaneous medication.

It is only after these validation steps for the molecule that the drug can eventually obtain marketing authorization (MA). Between 70% and 90% of drugs entering phase 3 are retained for a marketing authorization application.

Phase 4, long-term post-marketing follow-up

This additional step is a follow-up phase of the drug now on the market. Trials are carried out throughout the marketing of the drug and allow to deepen the knowledge of the product in real conditions of use and to detect rarer adverse effects that cannot be detected beforehand.

European regulations

The European regulation EU 536/2014 on Clinical Trials (CTR), which came into force in 2019, brings about a major change for European researchers. The main objectives of this important change in legislation are administrative simplification and harmonization at the European level.

Via a central EU portal, only one application (CTA, clinical trial authorization) will have to be submitted per clinical trial by the sponsor from all Member States taking

part in the clinical trial. Only one of the Member States will be designated by the sponsor as "Rapporteur Member State" which evaluates the application centrally and then issues a single opinion to the sponsor and the other Member States concerned.

Situation in the United States

The Food and Drugs Administration (FDA), an agency of the U.S. Department of Health and Human Services, protects public health by ensuring the safety, efficacy and security of human and veterinary drugs, vaccines and other biological products for human use, as well as medical devices.

Over the past several decades, the FDA has encouraged registration practices that would lead to clinical trials that better reflect the population most likely to use the drug if it is approved, primarily by broadening the eligibility criteria. Despite these efforts, difficulties in participating in clinical trials remain, and certain groups continue to be under-represented in many clinical trials, particularly older people.

It should be noted that the U.S. National Library of Medicine's Clinical Trials site is the official reference for reported clinical trials occurring anywhere in the world.

Ethics Committees

The notion of protection of persons in research practices appeared in the 1930s. After the Second World War, following the atrocious experiments carried out by Nazi doctors and Japanese war criminals, international awareness of the ethics of human experimentation for the protection of individuals began to emerge.

In 1947, the Nuremberg International Tribunal defined a code made up of ten rules, universally known as the "Nuremberg Code". This Code "recognizes" that experimentation on humans "for the good of society" is permissible and stipulates that "the voluntary consent of the human subject is absolutely essential". This was followed in 1949 by the International Code of Medical Ethics and in 1964 by the Declaration of Helsinki.

Most countries where clinical research is conducted currently have their own ethics committees, as do the countries of the European Community and the United States. Unfortunately, ethical approvals are often slow and still differ even within the European Union depending on the country (and sometimes even regionally). As a consequence, even in the time of Covid, some research is still considerably slowed down.

Eroom's law

Eroom's "law" is the observation that drug discovery becomes slower and more expensive over time, despite technological improvements, a trend first observed in the 1980s.

The cost of developing a new drug roughly doubles every nine years (adjusted for inflation). The current cost of developing a drug based on a new substance is estimated at one billion dollars! To contrast this with the exponential progress of other forms of technology over time, this conjecture has been deliberately called Moore's Law in reverse.

Self experiments

The famous geneticist George Church didn't want to wait for the results of the clinical trials. In what appears to be the first "citizen science" vaccine initiative, Preston Estep and at least 20 other researchers, technologists and science enthusiasts, many of whom are linked to Harvard University and MIT, have volunteered as "lab rats".

To develop a vaccine, the group, called the Rapid Deployment Vaccine Collaborative, or Radvac, studied reports of vaccines against SARS and MERS, two other diseases caused by coronaviruses. The goal is to find "a simple formula that you could make with readily available materials," says Estep. The vaccine, administered nasally, could create what is called mucosal immunity, that is to say immune cells found in airway tissues. This local immunity could be an important defence against SARS-CoV-2. But unlike antibodies that appear in the blood, where they are easily detected, signs of mucosal immunity may require a biopsy to be identified.

Clinical trials. How to advance medicine. Consent, a condition that is sometimes somewhat fictitious.

Without clinical trials: no new therapeutic methods, no new drugs. Every year, thousands of citizens engage in clinical trials to test new drugs.
Clinical trials must be conducted under the direction and supervision of a physician who must clearly inform the volunteer and obtain "informed" consent about the purpose of the research, its methodology, expected benefits, foreseeable constraints and risks, and the right to refuse to participate in research. Anyone who has consented to participate in research is free to withdraw consent at any time, and thus stop participating in the research.

The law makes it clear that the interests of those who participate in clinical research always outweigh the interests of science and society. In this area, we have moved from one extreme to the other, from abuses of human experimentation to provisions where even those who accept to take informed risks for the common good are not allowed to do so. Moreover, this extremely cumbersome legislation does not harm certain private interests, on the contrary. Only the big pharmaceutical companies are able to carry out the tests and to remunerate expensive and time-consuming legal and administrative staff. Small competitors are therefore eliminated (or absorbed), regardless of the value of their ideas.

Finally, it should be noted that for seriously ill people in hospital who are offered an experimental treatment, no matter what happens, informed consent is best

summed up as "We are offering you a treatment for which we think you have a better chance of survival (or improvement). You are free to take that chance or increase your risk of dying". Since the patient will still remain in the same facility if he or she refuses, even if the doctor is acting in perfect good faith, this limits the "free" character.

A question of patents and financial interests (Belgian example)

In 2018, 162 patent applications for drugs and/or vaccines were filed in Belgium (+30% compared to 2017), 507 new clinical studies were initiated and 1,399 drug studies were conducted. Last year, nearly 3.6 billion euros were invested in research in Belgium by (bio)pharmaceutical companies.

Three out of four clinical trials (77%) are organized and financed by the (bio)pharmaceutical companies themselves. The remaining 23% are carried out at the initiative of the academic or public sector. This proportion of private funding is one of the highest in Europe. Direct public investment in health is low. There is a high level of tax and other support for the privatization of research.

And the consequences for longevity research?

Measuring the impact of therapies for the elderly is complex. Obtaining their "informed" consent is often impossible, especially in the fight against neurodegenerative diseases.

Conducting clinical tests to fight against aging will be difficult, especially because deaths or accidents during clinical tests inspire fears. However, by definition, with or without treatment, mortality and morbidity will be higher in older subjects.

Yet, as we have seen with Covid research, enabling the oldest and most fragile people to live longer can become an almost absolute priority, even at considerable economic cost. Confidence is generally greater when research is carried out by non-profit organizations (public or not), leading to research results that can benefit everyone, without commercial involvement.

There are millions of young, old, and very old men and women who are willing to give informed consent (or who were willing to do so when they were still fully aware) for healthy longevity advances, even if they are not certain to benefit directly. In any case, in the event of experimental treatment, these people will benefit from very detailed follow-up, which will almost always be favorable to their health.

The good news of the month : Progress on Covid-19

In several countries, including France and even more so Belgium, overall mortality in 2020 will unfortunately be higher than in 2019.

Fortunately, at the end of this year, the huge efforts in vaccine research are now making it possible for products to be used no longer in the test phase, but on the general population, with a strong predicted efficacy and few side effects. Of the more than 300 vaccines in development worldwide, three are already being administered to the general population (two in China and one in Russia) and three are approaching this stage for the rest of the world (vaccines from consortia including Pfizer, AstraZeneca and Moderna, respectively).

No doubt, complex discussions will be held about choices, prices or anti-vaccine opposition. To get to where we are today may seem like a long road. However, the epidemic is less than a year old. Never before has a vaccine against a virus of the coronavirus family been made. The development of a new vaccine normally takes years.

A more "incremental" piece of positive news is that thanks to better knowledge of the disease and of therapies, especially in intensive care, mortality has decreased quite slowly but steadily for patients with the disease.

To learn more about it:

- *See in particular:* heales.org, sens.org, longevityalliance.org *and* longecity.org.
- Source of the image.