Who would accept a randomized trial in the context of covid-19 ?

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Although it has been shown that very few examples of treatable infectious diseases could benefit of randomized studies to guide their treatment, the use of randomized studies still remains controversial, especially in the currently mediatic domain of Covid-19 [1]. The methodologists use to consider that randomized trials are the best way to minimize the biases [2]. However even the inclusion criteria, such as the assessment of the diagnosis, the drugs standard doses, the duration of treatment, the stage of the disease, and the outcome evaluation criteria (hospitalization, ICU admission, death …) are not often respected and comparable [1]. This leads to a great confusion in the conclusion of different studies.

Another potential bias is generally not considered in the analysis of the studies: who are the patients who agree to participate in such studies? Did they receive clear information on the way the study will be conducted, on the drugs they could receive, etc.? Of course, they all sign an “informed consent” in which it is written that they received clear information, understood and agreed with it. But did they read several pages of medical technical text, or did they just trust their physician who proposed the enrolment in the study? As a first approach to answer these questions, we studied the acceptability of randomized trials in the treatment of Covid-19 infection.

During the two first weeks of October 2020, we conducted an anonymous opinion poll among the persons who spontaneously came to our institute for SARS-Cov2 testing. Those persons

were randomly interviewed by the nurses who made the nasopharyngeal sampling. The questions were shown and/or read to the patients without more comments. Three independent polls were conducted. The questions were:

Poll 1: "*Hydroxychloroquine seems to be efficient against Covid-19. According to this information, would you agree to participate in a therapeutic trial in which you would be chosen at random between a placebo and hydroxychloroquine, in order to review the effectiveness of this treatment?*".

Poll 2: "*Would you agree to participate in a therapeutic trial in which you would be chosen at random between a placebo, and a drug given intravenously for 10 days? The effectiveness of the drug is unknown, and renal failure is a frequent side effect*" (this refers of course to Remdesivir)

Poll 3: "*Would you agree to participate in a therapeutic trial in which you would be chosen at random between a placebo and Remdesivir, given intravenously for 10 days, knowing that : There is no current evidence for an efficiency of Remdesivir, except a weak decrease of the duration of hospitalization. There are renal side effects of Remdesivir in about 50 % of cases, according to the preliminary studies. The placebo will also be given intravenously although is established that intravenous catheters lead to local complications in more than 10 %?*"

Poll 1 involved 1355 persons. Their answer was YES for 690 persons (51 %), and NO for 533 persons (39 %), whereas 132 persons (10%) could not or did not want to answer the question.

Poll 2 involved 1167 persons. Their answer was YES for 280 persons (24 %), and NO for 745 persons (64 %), whereas 142 persons (12 %) could not or did not want to answer the question.

Poll 3 involved 546 persons. Their answer was YES for 54 persons (10 %), and NO for 468 persons (86 %), whereas 24 persons (4 %) could not or did not want to answer the question.

We can consider that the questions were short enough (without several pages of technical explanations), direct and quite easy to understand, as shown by a low percentage (4-12 %) of people who did not answer, most of whom due to difficulties to understand French. Under these conditions, only 51 % of the interviewed people would accept to participate to a study that compares Hydroxychloroquine to placebo. And when they receive a clear explanation on the drug administration constraints, and on potential adverse effects of a study drug, less than one person out of four would agree to participate to the study. This figure becomes as low as 10 % when clear explanations are given about the risks of the study drugs and of the intravenous way of administration for the placebo, regardless of the potential effectiveness of drugs.

According to these results, two important questions should be considered in the design of such randomized trials:

Can we really consider as ethical to suggest that a patient receive an intravenous placebo, according to the intrinsic risk of intravenous catheters [5, 6]?

How could we consider that these “volunteers” who agree to participate are representative of the global population? This pre-selection should be considered as a major bias and taken into account in the intention-to-treat analysis of the studies, which uses to consider the patients after their enrollment. The population who refuses this enrollment would need to be described.

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[2] Paul M. Has the door closed on hydroxychloroquine for SARS-COV-2? Clin Microbiol Infect. 2020 Oct 20 doi: 10.1016/j.cmi.2020.10.011 [Epub ahead of print]

[3] Mailhe M, Aubry C, Brouqui P, Michelet P, Raoult D, Parola P, Lagier JC. Complications of peripheral venous catheters: The need to propose an alternative route of administration. Int J Antimicrob Agents. 2020 Mar;55(3):105875. doi: 10.1016/j.ijantimicag.2020.105875. Epub 2020 Jan 8. PMID: 31926285.