Ethics Committees Reviews of Clinical Research Studies Applications in Italy During the Covid-19 Pandemic

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Introduction

Since the first identification in December 2019, the coronavirus disease 2019 (Covid-19) pandemic has spread from the city of Wuhan in China all over the world. The virus was first confirmed to have spread to Italy on 31 January 2020 and since then, as of April 2021, Italy results to be the 8th country in the world for absolute count of confirmed cases. Since the beginning of the pandemic, scientists and physicians from all over the world, Italy included, have been conducting many clinical studies involving affected patients in order to overcome the lack of information necessary in the battle against the newcoming virus. Indeed, the haste determined by the situation and the struggle for information threatened the possibility of lowering study quality as well as Ethical Committees review standards during the outbreak [4, 3]. Our investigation aimed to assess the impact of Covid-19 on clinical research studies quality submitted to Italian Ethics Committees in the period between April and July 2020.

Table 1. Italian Ethics Committees participation to the study

	No.	%
Italian Ethics Committees	91	100
Ethics Committees Participation Answers		
No answer to survey	64	70.3
Yes	15	16.5
Yes (No Covid-19 studies)	4	4.4
Not reachable	8	8.8
Study Applications	184	100
Ethics Committees Contribution by Region		
Lombardia	82	44.6
Liguria	32	17.4
Lazio	17	9.2
Puglia	17	9.2
Sardegna	14	7.6
Campania	11	6.0
Sicilia	11	6.0

Materials and Methods

All 91 Italian Ethics Committees have been contacted via email in order to collect information on the type and quality of Covid-related studies submitted to each Committee in the period between April and July 2020. Among the 91 Committees, 19 agreed to participate to the study (4 of them specified to have reviewed no Covid-related study), 64 did not answer to the survey, 8 resulted not reachable despite repeated telephone and email attempts at contact. In summary, 15 Ethical Committees from 7 different Italian Regions agreed to participate to the study and contributed with at least one case of Covid-related study, collecting an overall total of 184 study applications. Additional information on Italian Ethics Committees participation to the study are shown in Table 1. The Committees have been requested to fill in the information of the Covid-related reviewed studies in a spreadsheet file containing drop-down predefined options for any given column. The defined variables were: anonymous study Id, study design, mono or multicentric organization, choice of the comparison group, method of groups creation, study population, study objective and outcome, presence of sample size calculation and appropriateness with respect to the study objective, description of statistical analysis and appropriateness with respect to the study outcome, Ethics Committee final decision on study application.

Results

The 184 study applications included for the vast majority observational studies of various kind (n = 164; 89.2%) against 19 experimental studies, accounting for only 10.3% of the total; moreover, a meaningful percentage (39.5%) of the reviewed applications were part of multicentric studies. The main study population resulted to be adults (n=145; 78.8%) followed by pediatric (12.0%) and healthcare professionals (6.5%). 139 studies (75.5%) were designed as single-arm, thus the results obtained were mainly determined without comparison group.

Furthermore randomization have been rarely used as comparison group creation method (2.7%) and in general information on this specific topic resulted quite unclear, especially because biased by a consistently high percentage of missing answer (18.5%). The information relative to study objectives and outcomes, probably due to its intrinsic variability, resulted difficult to coerce into few predefined categories, as proven by the high percentages of "Other" responses collected (respectively 42.9% and 28.8%). Regarding study quality information we requested each Ethic Committee to declare if statistical analysis and sample size estimations were available and establish if the aforementioned were appropriate relatively to the single studies objective and outcome. The statistical analysis description was largely included in the applications (77.7% present; 73.4% present and appropriate) while the sample size calculation was in contrast very low represented (29.9% present; 25% present and appropriate). In summary, only 71 studies (22.4%) presented an appropriate statistical analysis description and a correct sample size determination. The vast majority of the studies were approved (n=127; 69.0%), while 34 (18.5%) were referred for modification and 6 (3.3%) were rejected; we highlight that for 17 studies this information was missing but can be traced back to the overall contribution of a single Ethic Committee.

Table 2. Applications approval rate and methodological quality

	No.	%
Study Applications	184	100
Committees Decision		
Approved	127	69.0
Referred for modification	34	18.5
Rejected	6	3.3
Not reported	17	9.2
Statistical Analysis Description		
Yes	143	77.7
No	41	22.3
Sample Size Determination		
No	128	69.6
Yes	55	29.9
Not reported	1	0.5
Appropriate use of statistical methodologies		
Statistical Analysis Description	135	73.4
Sample Size Determination	46	25.0
Both	41	22.3

As an additional consideration, we tried to analyze whether rejection or referral for modification, both conditions proving the review effort of the Committees aimed at study quality, were influenced by any of the variables collected. Using Fisher's exact test, we found a statistically significant association both between application approval and study population, with pediatric population-based studies more frequently rejected or suspended in comparison with non-pediatric ones (OR=0.2, IC 95%: 0.1, 0.6; p-value = 0.001), probably due to the greater caution generally related with pediatric healthcare, and between application approval and accurate statistical analysis description, where studies reporting a good quality statistical analysis resulted more likely to obtain Ehtics Committees approval (OR=11.0, IC 95%: 4.5, 27.9; p-value < 0.001). All the reviewed study characteristics are shown in detail in Table 2 and Table 3.

Conclusions

The main limitation of our study is the poor participation of the Italian Ethics Committees: we scored an already low overall 20.9% positive response rate, with only a raw 16.5% effectively involved in data contribution. Beyond the mere downsizing of the sample numerosity and the consequent poor representativity of the overall Italian situation, the scarce response in participation, against the Ethics Committees own self-interest, undermined the aim itself of the present study, making us unable to disprove the suspicion of quality review deterioration under the climate of urgency generated by Covid-19 pandemic in Italy.

We understood that some not responding Committees could have been overwhelmed by the amount of work caused by the pandemic; nevertheless, in such challenging historical period, both from a scientific and political perspective, the need for clear and reliable information is crucial. The pursue for information quality instead of quantity has been a problem during the pandemic, resulting in multiple cases with retractions and withdrawals of scientific papers [3]. We believe that science must be clear and open in its methodology because the general public needs to trustfully rely on its methods in order to overcome the challenge of the Covid-19 [1, 2]. Its our hope future studies on study quality assessment could experience broader participation in order to achieve these fundamental common goals.

Table 3. Characteristics of study applications evaluated

	No.	%
Study Applications	184	100
Study Design		
Prospective	71	38.6
Retrospective	46	25.0
Cross-Sectional	23	12.5
Experimental	19	10.3
Retrospective-Prospective	9	4.9
Diagnostic	9	4.9
Descriptive	6	3.3
Not reported	1	0.5
Study Population		
Adult	145	78.8
Pediatric	22	12.0
Healthcare professionals	12	6.5
Other population type	4	2.2
Not reported	1	0.5
Number of centers involved		
Monocentric	112	60.9
Multicentric	72	39.1
Groups creation methods		
Inclusion criteria	114	62.0
Researcher decision	12	6.5
Local feasibility	11	6.0
Other	8	4.3
Randomization	5	2.7
Not reported	34	18.5
Comparison group choice		
Single-arm	139	75.5
Parallel control group	32	17.4
Historical control group	9	4.9
Not reported	4	2.2
Study Objective		
Other	79	42.9
Prevalence estimation	63	34.2
Diagnostic exams validation	23	12.5
Treatment efficacy	18	9.8
Not reported	1	0.5
Study Outcome		
Percentage estimation	65	35.3
Other	53	28.8
Mortality and Survival	25	13.6
Quality of life	19	10.3
Time to heal	7	3.8
Therapeutical modifications	6	3.3
Viral load	5	2.7
Not reported	4	2.2

References

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