Ethical Innovation for Global Health:
Pandemic, Democracy and Ethics in Research
December 4 (Mon), 6 (Wed), 2023

Ethics of Placebo-Controlled Trials: Historical Analysis Including Experiences During the COVID-19 Pandemic

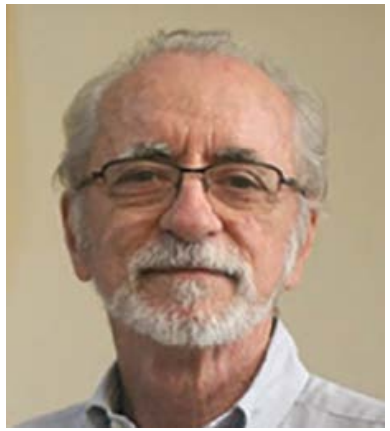
Chieko Kurihara, Dirceu Greco, Ames Dhai, Takeo Saio, and Hiroe Tsubaki

Post-Trial Access: Historical Analysis Considering the Experience of COVID-19 Pandemic

Chieko Kurihara, Dirceu Greco, and Ames Dhai

Authors ---- no conflict of interest

Placebo, Access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Placebo

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Historical analysis/Conflicting points

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Physician should provide
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CIOMS 2016
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minor increase above minimal risk

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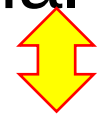
Typical case of establishment of “best proven therapy in the world” (not locally available)

Mother-to-childe transmission HIV prevention

- **Cons:** Placebo trial in developing countries ≒ Tuskegee study



- **Pros:** Placebo trial in developing countries for their health needs

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- **Pros:** Placebo trial in developing countries for their health needs

Twist and turns/Declining authority

- US FDA abandoned DoH (2000)

Because DoH does not permit placebo when proven intervention exists.

- Brazil / Latin America rejected DoH (2002*～)

Because DoH permits placebo when proven intervention exists with high threshold of risk of harm.

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Debates in various disease areas
Exclusion from “best proven intervention”

- Populations excluded from efficacy trials (pregnant, children, elderly, some intrinsic/extrinsic factors, ..)
- “best proven” becoming uncertain (“assay sensitivity”)
- “best proven” for surrogate endpoint but not for true endpoint
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No justification of placebo when proven intervention exists.

Case of Ebola outbreak

- Pros and Cons on placebo study when No Proven Intervention: WHO’s recommendation for emergency use of Unproven Intervention (MEURI).

Case of COVID-19

- End of 2020 to early 2021: global vaccine roll-out started based on emergency use authorization (EUA).
- WHO Ad Hoc Expert Group on the Next Steps for COVID-19 Vaccine Evaluation:

  "Countries with limited or no access to a known effective vaccine could thus ethically permit placebo-controlled trials of vaccines of potential relevance to them even if effective vaccines were already being marketed elsewhere."

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Strongly criticized by several ethicists;
Against the DoH: "best proven intervention (in the world)"

Conclusion

1. The meaning of “best proven intervention” must be clarified to be “intervention proven **in the world** to be the best”.
2. Policy for risk of placebo-controlled study when should be **risk minimization** (based on the wording in the 2016 CIOMS) and “**clinical equipoise**” or “**uncertainty**” should be the condition of comparative study, being rephrased in wording understood by and shared with physicians, patients, and the public.

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- **Downgraded** in 2004, 2008, 2013, to be the item in a protocol reviewed by the ethics committee and informed consent form for candidate participants.
- COVID-19 has revealed the inequality in the distribution of the result of science, typically the availability of vaccines.

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Our conclusion

- Post-trial access must be assured not only for trial participants, but for **those who most in need in the world**.

Challenges to be overcome

- Patent monopoly and insufficient technology transfer: critical part of the obstacles to post-trial access for all.
- TRIPS Doha Declaration in times of HIV/AIDS pandemic and COVAX and TRIPS waiver in COVID-19 along with expanding production capacity in MICs and LMICs are “Good Start”, but not yet solution.
- Ethical norm of “post-trial access” must be described as a goal to be shared and achieved in a global society.