Placebo verssus comparator vaccine in clinical trials

Pieter Neels, MD

Placebo control permissible when no safe and effective vaccine (UNAIDS 2012) or no established effective intervention (EEI) exists (CIOMS 2002)

- Permissible when effective vaccine/ intervention exists when
  - Needs compelling justification (CIOMS 2002)
  - Efficacy demonstrated against *particular viral strain* and vaccine may not be effective against virus prevalent in study population (UNAIDS 2012)
  - Efficacy demonstrated for *particular population* and biological conditions prevailing in original study can't be applied to study population (UNAIDS 2012)
  - Data collected under circumstances unlike those of the study pop (CIOMS 2002)
  - Results yielded would not be scientifically reliable (CIOMS 2002)
  - Participants exposed to temporary discomfort, no serious or irreversible harm, no serious adverse consequences (CIOMS 2002)
  - Both arms must receive preventive interventions (UNAIDS 2012)
  - Intervention intended for use in a country/ community where an EEI is not available (and unlikely to become so), is responsive/ relevant to the health needs/ problems of the population (CIOMS 2002)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Reflection paper

Placebo and active comparator

Lack of access of patients in communities within, or outside of, the EEA, to the **EEA-licensed** (or equivalent) comparator **cannot be a justification** to withhold this treatment option to those patients when participating in a trial regardless of the reasons for the lack of access (e.g. no reimbursement, no national marketing authorisation). **Regardless of the location of the trial**, all patients participating in these trials should receive **the same or a similar standard of care** and comparable treatment options as trial participants within the EEA.

Example

Sponsor X wants to develop a new PnCV, but **without** Capsule Poly-Saccharides (PS), but **with** capsule proteins,

⇒ No head to head comparison between the new vaccine and the old ones, based on the WHO guideline non-inferiority on immunogenicity is possible

Superiority for the new vaccine is claimed, (80-90% of **all** PnC strains will be prevented [instead of 10, 13, 15…])

- In those countries where PnCV are in use, IPD as clinical endpoint is (probably) not feasible, as IPD becomes too rare.
  ⇒ In industrialised countries endemicity 0,5-5 x 10.000/y
- Extrapolation of mucosal disease (AOM, Rx proven pneumonia) to IPD is difficult to accept…

VIEWPOINT

Ethics, Regulation, and Comparative Effectiveness Research
Time for a Change

By Richard Platt, Nancy E. Kass and Doven McGraw

In JAMA 13 March 2014

Rationale to support comparative effectiveness research

- In any health system, systematic evaluation of established practices should be routine and continuous
- Increasing availability of data arising from electronic health information systems
- Observation of outcomes of chosen practices are often heavily biased
- For many health care questions, it is important to intervene by systematically varying care, which allows for less biased observations of its impact

Where is the line ?
What are the implications ?

- When does evaluation and quality check of clinical practices become research ?
- What oversight is needed ?
- What level of transparency is needed ?

Furthermore, one example of a broader oversight approach "rejects the assumption that clinical research and clinical practice are fundamentally different enterprises," and suggests that all stakeholders share a moral obligation to contribute to learning and improvement of care.[8] This ethical framework suggests that regula-

What are the implications of this paradigm shift to vaccinology ?

- Calls for more robust impact studies in the post-licensure phase
- Robust = RCT = utilizes randomization and controlling
- Examples Cluster randomized study on

  HPV2 vs. HPV4

  LAIV vs. TIV/QIV in children

  TIV/QIV vs. nothing in elderly in areas where childhood influenza vaccine coverage is high

Religious Concerns about Vaccines

Vaccine 31 (2013) 2011–2023

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

What the World's religions teach, applied to vaccines and immune globulins

John D. Grabenstein*,[1]

Merck Vaccines, 770 Sumneytown Pike, WP97-B364, West Point, PA 19426, USA

ARTICLE INFO

Article history:
Received 20 October 2012
Received in revised form
21 December 2012
Accepted 7 February 2013
Available online 26 February 2013

ABSTRACT

For millennia, humans have sought and found purpose, solace, values, understanding, and fellowship in religious practices. Buddhist nuns performed variolation against smallpox over 1000 years ago. Since Jenner developed vaccination against smallpox in 1796, some people have objected to and declined vaccination, citing various religious reasons. This paper reviews the scriptural, canonical basis for such interpretations, as well as passages that support immunization. Populous faith traditions are considered,

Objections to immunization attributable to religious beliefs

1. Violation of prohibitions against taking life,
2. Violation of dietary laws, or
3. Interference with natural order by not letting events take their course

Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health

Grabenstein Vaccine 31 (2013) 2011–2023

Concern about Violation of prohibitions against taking life

- RA 27/3 strain rubella vaccine:
  - Wild type virus from products of conception in woman who had rubella and elected abortion

Viruses Grown in Diploid Cell Lines Derived from Aborted Fetuses

- MRC-5
- WI-38
- Well characterized
- Used to grow viruses that have been in 100s of millions of doses of vaccines
- No safety issues

Reasons Why Vaccines Made With Fetal Origin Materials are Acceptable

- Abortions were not performed with the purpose of obtaining materials used to produce vaccines
- None of the fetal products are in the final vaccine preparations
- No additional abortions needed to produce vaccines

Grabenstein Vaccine 31 (2013) 2011– 2023
Grabenstein JD. Where Medicine and Religion Intersect.
Ann Pharmacother 2003;37:1338-9
Zimmerman RK. Vaccine 2004;22(31-32):4238-44.

Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health

2008 Official Roman Catholic Teaching

- Being immunized does not involve any sharing in immoral intention or action of others
- Parents have a moral obligation to provide for the life and health of their children by means of immunization

Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

Grabenstein Vaccine 31 (2013) 2011– 2023

Pork Origin issues

1. Components have been sufficiently transformed from original pork origins,
2. The minute quantities per dose administered (e.g., hydrolyzed
3. gelatin, trypsin) invoke exceptions based on dilution, or
4. Vaccine is intended for medicinal purposes and not a matter of ingestion, to which dietary rules apply.

Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

Grabenstein Vaccine 31 (2013) 2011– 2023

Porcine Origin

Jewish:

- "Drugs of Porcine origin are derived from the Pancreas which, as extracted, is not edible in the food sense" *Principle of transformation.*
- Injectable medications are not subject to kosher rules

Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

Grabenstein Vaccine 31 (2013) 2011– 2023

Porcine Origin

Muslims: "The Gelatin formed as a result of the transformation of the bones, skin and tendons of a judicially impure animal is pure, and it is judicially permissible to eat it." *1995 decision by the Islamic Organization for Medical Sciences in English and Arabic*

Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

www.vaccinesafety.edu/Religion.htm

Case study

Case Study – role play

- Read the case (aloud?) in your groups (5-10 mins)
- Choose either (1) researcher/sponsor; (2) IRB or (3) activist

1. Cluster in those groups + plan your position (30 mins)
2. Come together for a debate chaired by REC chair (30 mins)
3. All decide on ethical standards (30 mins)

- Write up brief (2page) record on the decisions (10 mins?)
- Place in BOX at rear of this room as soon as possible
- Record which group you are
- Summary is Monday morning
- *Remember all case studies have missing information. You will have to make assumptions. Make the assumptions explicit*