

Evidence, Equipoise and Methodological Absolutism

Professor Søren Holm, BA, MA, MD, PhD, DrMedSci
University of Manchester & Universitetet i Oslo

MANCHESTER
1824

The University of Manchester



UiO : **University of Oslo**

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Overarching question

How can / should we generate high quality evidence of efficacy of a new drug in the absence of equipoise?

The basic structure of the problem

1. Clinical equipoise generally accepted as a requirement for the justifiability of conducting a Randomised Controlled Trial (RCT)
2. RCT evidence 'required' for regulatory approval
3. RCT evidence (rightly) seen as high quality evidence of efficacy
4. High quality evidence of efficacy required for overall funding decisions in some health care systems

1-4 lead to an impasse if clinical equipoise is absent and we are 'methodological absolutists'

Further complication

Practically impossible to run a valid RCT if:

1. There is no personal clinician equipoise and/or
2. There is no personal patient equipoise and
3. Treatment allocation is (or becomes) obvious

(1 or 2) and 3 → Differential withdrawal in control and intervention groups → Undermines validity of the study

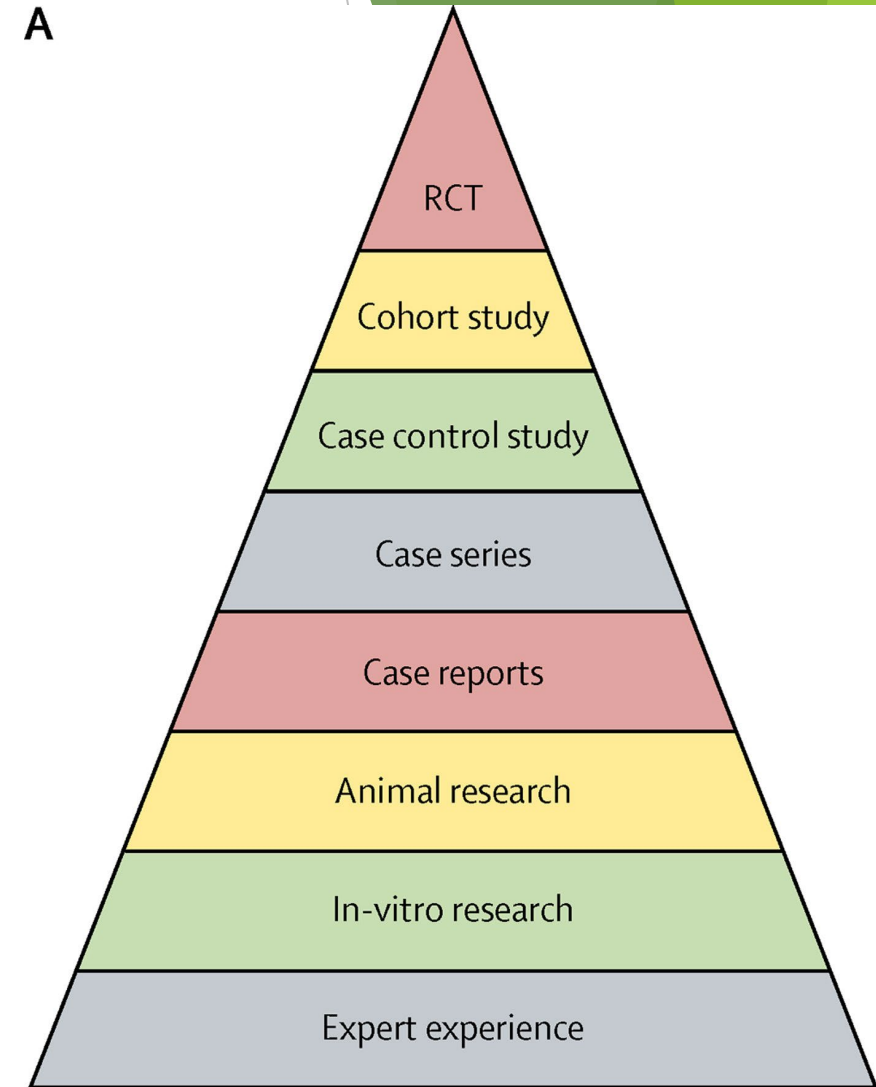
But, it would (obviously) be unethical to force participants to stay in a trial against their will

Regulators and third party health care funders are right to require high quality evidence

There is also an ethical imperative to generate high quality evidence, e.g. as the evidential basis for patient choice

But although (good) RCT evidence is high quality, it is not the only type of high quality evidence, despite the impression given by the Evidence Based Medicine evidence hierarchies

If it is not possible to conduct a RCT then we need to take another look in the methodological toolbox



Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *The Lancet*. 2017;390(10092):415-23.

What should regulators do?

Engage actively with researchers and research sponsors to design studies that are likely to produce evidence that can clear the regulatory threshold

Many examples in the orphan and hyper-orphan context (where the issue is primarily an issue of numbers available to recruit)

Similar flexibility must be employed in other contexts where a RCT **cannot*** be performed

** Quite important that what we are discussing is not a context where a RCT is difficult to perform, but a context where it is impossible to perform an ethically acceptable and methodologically valid RCT*

'Ideal' scenario

Existing disease specific cohort with longitudinal follow-up and good data registration

Or

Well organised public health care system with strong EPJ systems and strong data capture (e.g. the Nordic countries)

Enables the conduct of high quality case-control studies, including capture and analysis of data from 'compassionate use' cases

May also support analysis of 'natural experiments' where drug is prescribed in some health care institutions and not in others

Ethical issue: Data access without consent*

*Ploug and Holm's 'Meta-consent' framework may solve this issue. Ploug T, Holm S. Meta consent: a flexible and autonomous way of obtaining informed consent for secondary research. *BMJ*. 2015;350. doi: <https://doi-org.manchester.idm.oclc.org/10.1136/bmj.h2146>

Soft and hard endpoints

In research where the endpoints are 'soft' it is especially important that the data relating to the controls in a case control study are (or has been) collected prospectively to avoid bias

Summary

Lack of clinical and/or patient equipoise can create a situation where it becomes ethically unacceptable and methodologically impossible to conduct a valid RCT

In such situations regulators (and ethics committees) have an obligation to:

1. Be flexible in their demands for high quality evidence, and
2. Engage constructively with researchers and research sponsors in designing studies that can produce evidence to the standard required by the (flexible) regulator

All of this follows from one of the basic axioms of deontic logic (the logic of normative statements), i.e. 'Ought implies can'

It is highly preferable if the impossibility of a RCT is identified before we try running one!