UMC Utrecht

Ethics of pragmatic trials: *Considerations for informed consent*

KCE Trials Symposium, 28 November 2017

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- Assessing existing processes, methodologies, and key research issues;
- Proposing innovative trial designs and assessing the value of information;
- Proposing and testing innovative analytical and predictive modelling approaches;
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- Creating new decision making support, and building tools to allow for the evaluation of development programmes and use in the assessment of the value of introducing new treatments;
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PragMagic Launch: an innovative tool to

Why might pragmatic trials be morally problematic?

Ethical Guidelines for Clinical Research

- 1947: Nuremberg code
- 1964: Declaration of Helsinki (WMA)
  - Latest revision: 2013 (Fortaleza)
- 1975: Good Clinical Practice (EU Directive)
  - Latest revision: 2014
- 1982: CIOMS (WHO)
  - Latest revision: 2016
- 1997: Council of Europe: Oviedo convention
- NL: WMO (1998)
  - Latest revision 2017

7 Requirements for Determining Whether a Clinical Trial is Ethical

1. Social or Scientific Value
2. Scientific Validity
3. Fair subject Selection
4. Favorable Risk/Benefit ratio
5. Independent review
6. Informed consent
7. Respect for participant (enrolled/potential)

Pragmatic Trials Raise New Questions

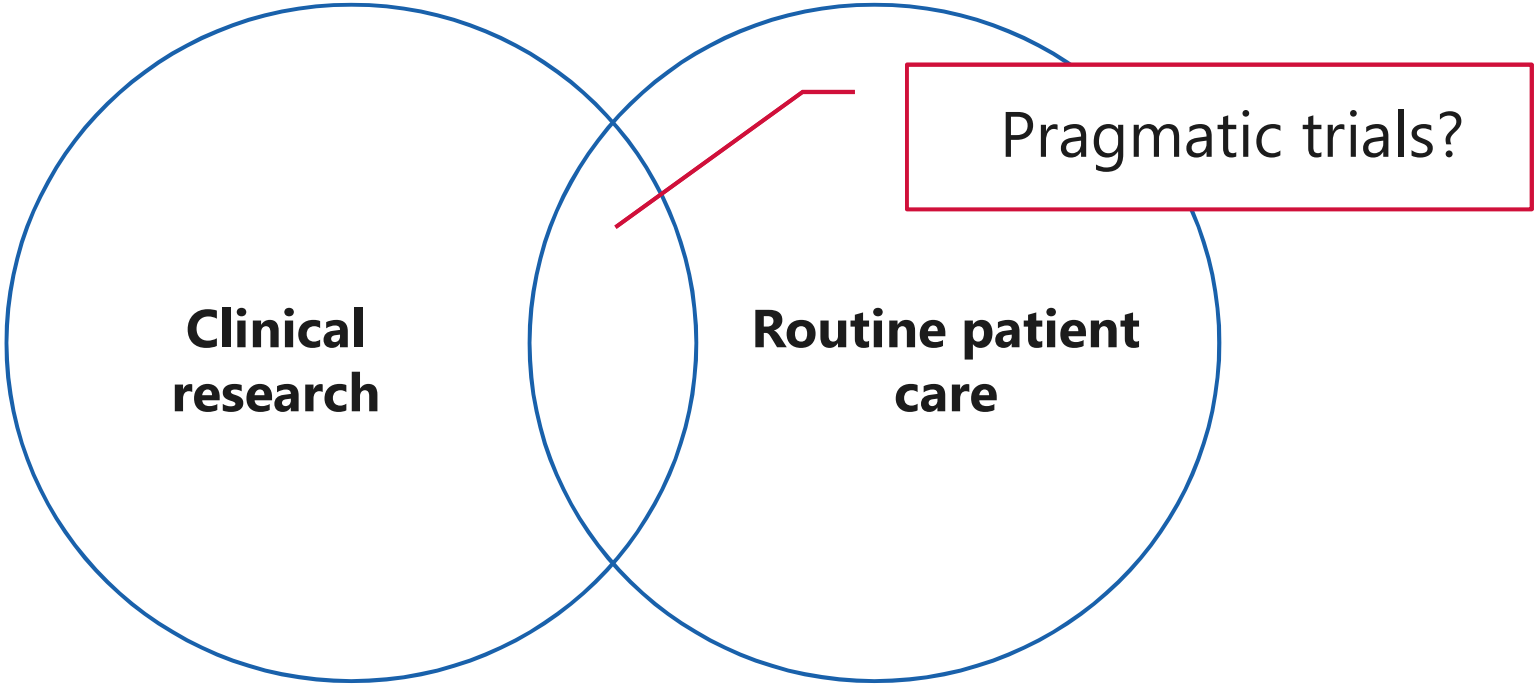
- What level of (regulatory/ethics) oversight do pragmatic trials require? → judge by standards for care or research?

- What additional risks do patients face in a pragmatic trial (on top of usual care)?

- May IC procedures be modifed/waived in pragmatic trials?

Kalkman et al. *Pragmatic randomized trials in drug development pose new ethical questions: a systematic review*. Drug Discov Today (2015).

Moral distinction between research and care?



Stakeholder interviews (n = 34)

What ethical issues have you come across or do you foresee when designing or conducting a pragmatic trial?

What is your view on pre-market authorization pragmatic trials?

Kalkman et al. *Stakeholders' views on the ethical challenges of pragmatic trials investigating pharmaceutical drugs*. Trials (2016).

Salford Lung Study (GSK, results published Sep 2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

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ABSTRACT

BACKGROUND

Evidence for the management of chronic obstructive pulmonary disease (COPD) comes from closely monitored efficacy trials involving groups of patients who were selected on the basis of restricted entry criteria. There is a need for randomized trials to be conducted in conditions that are closer to usual clinical practice.

METHODS

In a controlled effectiveness trial conducted in 75 general practices, we randomly assigned 2799 patients with COPD to a once-daily inhaled combination of fluticasone furoate at a dose of 100 μg and vilanterol at a dose of 25 μg (the fluticasone furoate–vilanterol group) or to usual care (the usual-care group). The primary outcome was the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial. Secondary outcomes were the rates of primary care contact (contact with a general practitioner, nurse, or other health care professional) and secondary care contact (inpatient admission, outpatient visit with a specialist, or visit to the emergency department), modification of the initial trial treatment for COPD, and the rate of exacerbations among patients who had had an exacerbation within 3 years before the trial, as assessed in a time-to-event analysis.

RESULTS

The rate of moderate or severe exacerbations was significantly lower, by 8.4% (95% confidence interval, 1.1 to 15.2), with fluticasone furoate–vilanterol therapy than with usual care (P=0.02). There was no significant difference in the annual rate of COPD-related contacts to primary or secondary care. There were no significant between-group differences in the rates of the first moderate or severe exacerbation

Phase 3b comparative effectiveness trial!

Vestbo et al. *Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice*. NEJM (2016).

Some concerns

- Less controlled conditions might create safety concerns
- Comparison with suboptimal usual care compromises clinical equipoise
- Modified or waivers of consent infringes patient autonomy (and public trust!)
- Minimal interference drives arms to equivalence (minimal knowledge value)
- For pre-market trials: concerns are heightened

Caveats

- Highly exploratory nature
- Not all respondents had experience with pragmatic trials
- Different understanding of what a pragmatic trial might look like
- One respondent: *"what about the harms if we did not do these trials?"*

How to balance value/benefits of pragmatic trials with these issues?

Case study:
Informed consent process

Are there any good arguments that ethically justify deviations from IC requirements for RCTs?

What do the regulations require?

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

ICH Good Clinical Practice Guidelines E6(R1), 1996.



What consent modifications do the regulations allow?

EU Directive

Pre-market: no modifications allowed

Post-market: "simplified means" allowed for cluster trials (sounds like opt-out)

FDA regulations: pre-market → no modifications allowed

OHRP: post-market → waivers allowed under certain conditions

Analysis of literature and regulations

Agreement on at least 3 conditions that would permit modifications:

1. The research involves minimal risk
2. The research is impracticable with regulatory consent
3. The modification still allows patients a say in their care

Table 1 – Criteria to assess the acceptability of consent modifications for early pragmatic trials (EPTs).

Criteria	Definitions	Premarket EPT (phase III)	Postmarket EPT (phase IV)
Is the study a minimal-risk study?	Are the two (standard-of-care) treatments generally regarded as having similar *ex ante* risk–benefit profiles?	No. Since no independent review by a regulatory authority has been performed, more than minimal risk in face of uncertainty seems a more reasonable view (risks and benefits of compared treatments cannot be assumed to be similar).	Maybe. It depends on the data available. The new drug could be seen as having a better risk–benefit profile, or it could be seen as more risky because of lack of market experience. Will require case-by-case judgment.
Is the study impracticable with regulatory consent?	*Cause*: Is the loss of data quality caused by selection bias or inability to recruit a sufficient number of patients and can this loss be reasonably attributed to regulatory consent?	Will require case-by-case judgment. It will be important to establish that the quality loss is caused by extrinsic effects of regulatory consent.	Will require case-by-case judgment. It will be important to establish that the quality loss is caused by extrinsic effects of regulatory consent.
	Effect: Is the expected loss of data quality so extreme that the trial is not worth performing?	Will require case-by-case judgment.	Will require case-by-case judgment.
	Alternative: Apart from modifying regulatory consent, are there no available means or resources that may be reasonably expected to counter the loss of data quality?	Maybe. Although the majority of premarket EPTs is industry sponsored, indicating some sort of availability of resources to enhance recruitment without compromising too much on real-world conditions.	Maybe. Although most postmarket EPTs will still be industry driven, increasing the likelihood of resolving data-quality issues with resources.
Does waiving or altering regulatory consent respect patient expectations?	Does waiving or altering regulatory consent respect any legitimate expectations patients may have of having a say in whether tested treatments are received inside the trial versus outside the trial or to be informed about how treatment allocation occurs?	No. The test intervention remains "experimental" when it concerns novel, unapproved treatments, regardless of explanatory or pragmatic designs. Thus, patients always have legitimate reasons to expect to be informed about all trial and intervention aspects and to decide whether to participate.	Maybe. Treatments are no longer "experimental," since they are accepted—i.e., on the market but presumably not yet in widespread use. Patients have a reasonable expectation of being informed about relatively new treatments in a trial and in what ways the compared treatments differ in terms of side-effects, use, and so on. Will thus require case-by-case judgment.
Overall assessment	• Are all three conditions likely to be met? • Is a waiver of regulatory consent ever justified? • Are alterations to regulatory consent ever justified?	• No premarket EPT will meet all three criteria. • No premarket EPT can be conducted with a waiver of consent. • No premarket EPT can be conducted with alterations to regulatory consent.	• Some postmarket EPTs could to some extent meet all three conditions. • No postmarket EPT can be conducted with a full waiver of informed consent. • Some postmarket EPTs may be conducted with altered, simplified informed consent.

Waiver, modifications or none?

	Pre-market EPTs	Post-market EPTs
Are all 3 conditions likely to be met?	No	Some post-market EPTs might, to some extent
Is a waiver of regulatory consent ever justified?	No	No
Are modifications to regulatory consent ever justified?	No	Perhaps

Implications for informed consent in (early) pragmatic trials

- Salient differences between pre-market and post-market EPTs versus standard of care pragmatic trials
- No modifications permissible for pre-market EPTs
- Some post-market EPTs might be conducted with consent obtained through simplified means

Kalkman et al. *Ethics of Informed Consent for Pragmatic Trials with New Interventions*. Value Health (2017); Kalkman et al. *Series: Pragmatic trials and real world evidence: Paper 4. Informed consent*. J Clin Epidemiol (2017).

Side notes

- Question remains what alterations might exactly look like
- Does not mean that phase III and early phase IV trials should not be pragmatic (they should!)
- But the normative consequences of alterations to trial ethics guidance ought to be considered

Thoughts for the future of (early) pragmatic trials

- Goals of pragmatic trials might cause tension with rules and regulations for RCTs (R/B, equipoise, IC)

- Given importance of RWE, social imperative to reconcile where possible

(1) Many way to increase pragmatism (PRECIS!)

(2) Delineate areas demanding early pragmatic evaluations

(3) Point towards opportunities in regulations

(4) Demarcate ethical limits of pragmatism with criteria of minimal risk, impracticability and patient expectations

Thank you for your attention!

Special thanks to:

Ghislaine van Thiel (UMC Utrecht)
Hans van Delden (UMC Utrecht)
Rick Grobbee (UMC Utrecht)
Scott Kim (Dept. Bioethics, NIH)

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