Ton de Boer – Chair

CBG MEB

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

The future of clinical rials: evidence generation for regulatory decision making

Pragmatic RCT

GOEDE MEDICIJNEN GOED GEBRUIKT

Declaration of interests

Professor of Pharmacotherapy (pharmacoepidemiologic research)

Former Chairman of the Dutch Reimbursement Committee

Chairman of the Dutch Medicines Evaluation Board (MEB), since August 1st 2017.

This talk reflects my personal views; I am being inspired and challenged by many colleagues within the MEB and university.

Pre-marketing randomized trials

- Gold standard from the clinical research paradigm
- Limitations
  - Highly selected patients groups
  - Relative short follow up
  - No real world data
  - Surrogate endpoints

→ Limited knowledge of intended and unintended drug effects

Problems post marketing

- After marketing we learn more about the safety of drugs “not” about the effectiveness
  - Thus after marketing the B/R ratio “always” becomes worse
- Often we do not know the value of a new drug compared to existing therapies

Needs

- Real world evidence (RWE)
  - Want to know how drugs perform in routine clinical pratice
- Comparative effectiveness
  - Need for adequate data to guide choices among therapeutic alternatives
- MEB regulator: need for valid RWE data. “Unbiased” effect estimates to be able to change drug labels

What is Real World Data?

Available online at www.sciencedirect.com

ScienceDirect

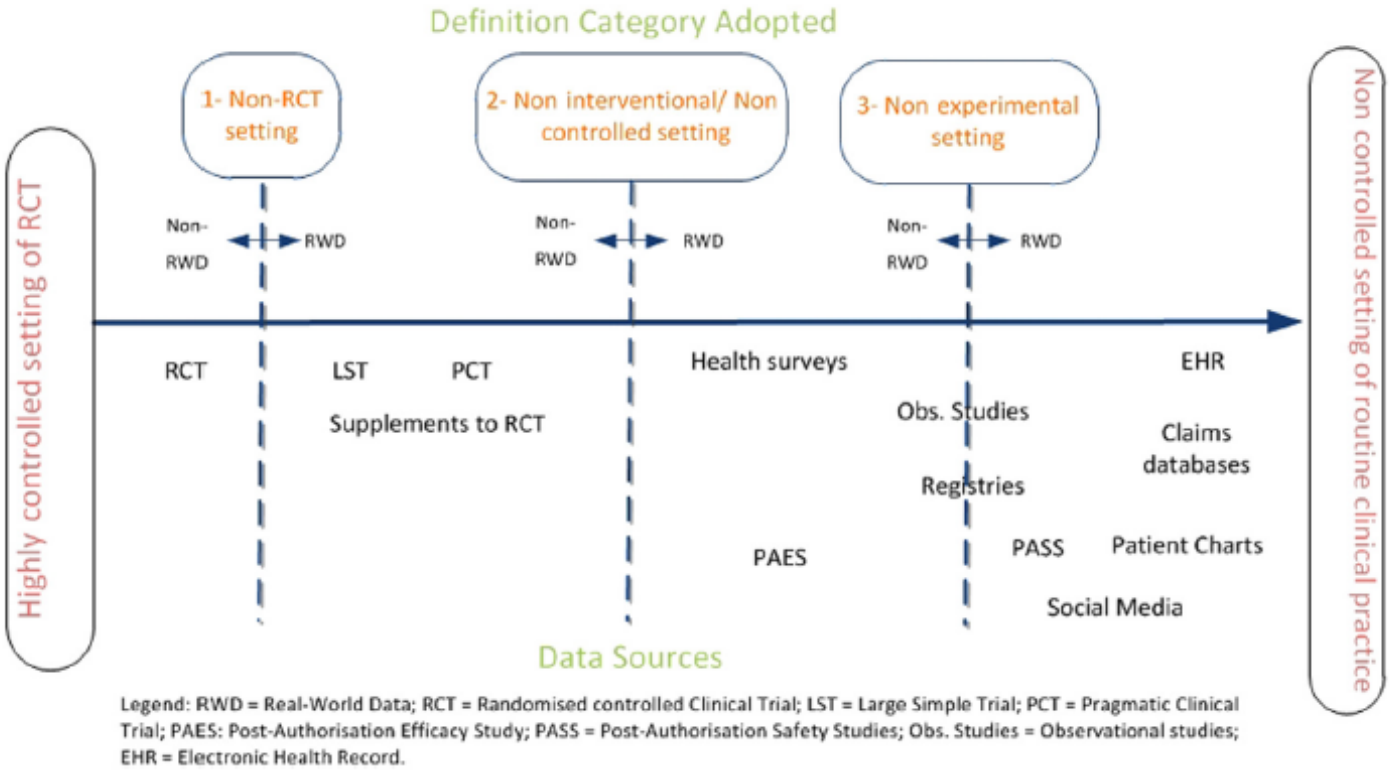
journal homepage: www.elsevier.com/locate/jval

What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews

Amr Makady, MSc[1,2,], Anthonius de Boer, MD, PhD[2], Hans Hillege, PhD[3], Olaf Klungel, PhD[2], Wim Goettsch, PhD[1,2], (on behalf of GetReal Work Package 1)*

[1]*The National Healthcare Institute, Diemen, The Netherlands;* [2]*Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands;* [3]*Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands*

Spectrum of terms are being used



Legend: RWD = Real-World Data; RCT = Randomised controlled Clinical Trial; LST = Large Simple Trial; PCT = Pragmatic Clinical Trial; PAES: Post-Authorisation Efficacy Study; PASS = Post-Authorisation Safety Studies; Obs. Studies = Observational studies; EHR = Electronic Health Record.

Fig. 2 – Data spectrum in relation to RWD definition categories. EHR, electronic health record; LST, large simple trial; observational; PAES, postauthorization efficacy study; PASS, postauthorization safety study; PCT, pragmatic clinical trial randomized controlled trial; RWD, real-world data.

RWD not collected in conventional RCTs?

Table 1 – ISPOR, ABPI, RAND Corporation, and IMI-GetReal definitions for RWD.

Term and source	Definition
RWD (ISPOR [7])	Data used for decision making that are not collected in conventional RCTs.
RWD (ABPI [8])	For the purposes of this guidance, "RWD" will refer to data obtained by any non-interventional methodology that describe what is happening in normal clinical practice.
RWD (RAND [9])	"RWD" is an umbrella term for different types of health care data that are not collected in conventional RCTs. RWD in the health care sector come from various sources and include patient data, data from clinicians, hospital data, data from payers, and social data.
RWD (IMI-GetReal [10])	An umbrella term for data regarding the effects of health interventions (e.g., benefit, risk, and resource use) that are not collected in the context of conventional RCTs. Instead, RWD are collected both prospectively and retrospectively from observations of routine clinical practice. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes, and health-related quality of life. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.

ABPI, Association of the British Pharmaceutical Industry; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; RCT, randomized controlled trial; RWD, real-world data.

RWD should be collected in premarketing randomized controlled trials

- Obligatory prognostic factors and patients outcomes (defined in the case record forms)

- Electronic health records
- Diaries
- Applications counting number of footsteps
- Mobile Health APPS
- Data from a (new) registry
- (Costs)
- Etc etc

Postmarketing RWD should be collected in randomized controlled trials

- Pragmatic or (stepped wedge) cluster randomized (blinded) controlled trials
- Randomization of patients or practices in daily practice (general practitioner, specialist, pharmacist)
- Prognostic factors and patients outcomes from routinely collected electronic health records
- Possible to evaluate **clinically relevant** intended and unintended effects (including mortality)

Problems to conduct pragmatic RCTs

HEALTH TECHNOLOGY ASSESSMENT

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The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials

Tjeerd-Pieter van Staa, Lisa Dyson, Gerard McCann, Shivani Padmanabhan, Rabah Belatri, Ben Goldacre, Jackie Cassell, Munir Pirmohamed, David Torgerson, Sarah Ronaldson, Joy Adamson, Adel Taweel, Brendan Delaney, Samhar Mahmood, Simona Baracaia, Thomas Round, Robin Fox, Tommy Hunter, Martin Gulliford and Liam Smeeth

Recruitment of GPs and patients appeared to be highly problematic

A major problem was the informed consent procedure

Will lead to selected patient groups

Simvastatin versus atorvastatin and immediate antibiotics versus deferred or non-use

EU regulations: definition of low intervention trials

Box 1: Definition of low intervention clinical trials* according to EU regulations[32]

A low intervention clinical trial is one that fulfils all the following conditions:

- The investigational medicinal products, excluding placebos, are authorised
- According to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is evidence based and supported by published scientific evidence on their safety and efficacy in any of the member states concerned
- Additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the participants compared with normal clinical practice in any member state concerned

*Low risk pragmatic randomised controlled trials randomising at participant level

EU regulations: informed consent is necessary when patients are randomized

I

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Low risk pragmatic trials do not always require participants' informed consent

Clinical trial regulations should remove unnecessary obstacles for the conduct of pragmatic trials assessing the comparative effectiveness of medicines posing no or minimal risk to participants, say **Rafael Dal-Ré and colleagues**

Rafael Dal-Ré *senior investigator*[1], Cristina Avendaño-Solà *head*[2], Brigitte Bloechl-Daum *professor*[3], Anthonius de Boer *professor*[4], Stefan Eriksson *associate professor*[5], Uwe Fuhr *professor*[6], Søren Holm *professor*[7], Stefan K James *professor*[8], Robert J Mentz *investigator*[9], Emilio Perucca *professor*[10], Frits R Rosendaal *professor*[11], Shaun Treweek *professor*[12]

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(Published 27 March 2019)

Is informed consent always necessary when performing a randomized trial with authorized drugs?

- "Natural" randomisations happen all the time in daily practice
- There should be "equipose"
- Low risk trials
- High social value
- When informed consent seriously hampers the execution of a pragmatic RCT

Outside the EU: Modifications and waivers of informed consent in the context of a randomized study

Table 2| **Modifications and waivers of informed consent in Canadian and US regulations and in Council for International Organizations of Medical Sciences (CIOMS) guidelines**

Canadian regulations[29]	*US regulations*[30]	*CIOMS guidelines*[31]
The research ethics board may approve research that involves an alteration† to the requirements for consent . . . if is satisfied, and documents, that all the following apply:	An institutional review board [ethics committee] may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the board finds and documents that:	A research ethics committee may approve a modification or waiver of informed consent to research if:
the research involves no more than minimal risk to the participants	the research involves no more than minimal risk‡ to the participants	the research would not be feasible or practicable to carry out without the waiver or modification
the alteration to consent requirements is unlikely to adversely affect the welfare of participants	the waiver or alteration will not adversely affect the rights and welfare of the participants	the research has important social value, and
it is impossible or impracticable to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required	the research could not practicably be carried out without the waiver or alteration, and	the research poses no more than minimal risks to participants
in the case of a proposed alteration, the precise nature and extent of any proposed alteration is defined and	whenever appropriate, the participants will be provided with additional pertinent information after participation	
the plan to provide a debriefing (if any), which may also offer participants the possibility of refusing consent and/or withdrawing data and/or human biological materials		

Feasability of pragmatic RCTs without informed consent I

- Equipoise situations (follow up study of the BMJ manuscript)
  - Existing guidelines?
- Research protocol necessary with input from health care practitioners and patients
- Assessment of the protocol by an ethics committee
- General practitioners or specialists willing to participate in pragmatic RCTs
- Software necessary to perform randomization
- In an environment of electronic health records (e.g. PHARMO, CPRD)

Acceptability of pragmatic RCTs without informed consent I

- "Natural" randomisations happen all the time in daily practice
- There should be equipose
- Low risk trials
- High social value
- When informed consent seriously hampers the execution of a pragmatic RCT

Acceptability of pragmatic RCTs without informed consent II

- The standard paradigm in research ethics—where a sharp distinction is made between research and care—needs to be challenged.
- Crucial that besides the randomisation procedure patients will only receive standard care
- Debriefing patients after they have finsihed taking part?
- General statement for patients that their GP participates in research to improve care

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