EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Generating the right data

Randomised, observational, prospective, retrospective,…

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The views expressed are personal views and not necessarily the views of CBG-MEB or EMA.

Overview

- Introduction & scope.
- Clarifying the Single Arm Trial Reflection Paper.
- Widening the design space for clinical trials (research).
- Suggestions to further progress.

Introduction: The RCT……

Intended **and unintended effects of therapy***

Intended effects of therapy

- RCT
- Prospective follow-up
- Retrospective follow-up
- Case-control
- Anecdotal

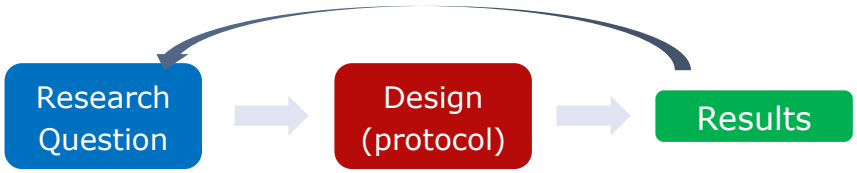
Discovery and explanation

- Anecdotal
- Case-control
- Retrospective follow-up
- Prospective follow-up
- RCT

*(Unknown) Adverse effects are "unintended", usually not associated with indication: no "confounding by indication"-> observational evidence can be strong.

J.P. Vandenbroucke (2008). Observational Research, Randomised Trials, and Two Views of Medical Science, PLoS Medicine

Introduction



RCTs are *controlled experiments*

- Randomisation facilitates causal attribution of effect.

Controlled:

- High level of standardisation and data quality (signal to noise ratio)

Strong basis to properly estimate variability / uncertainty (within the trial)

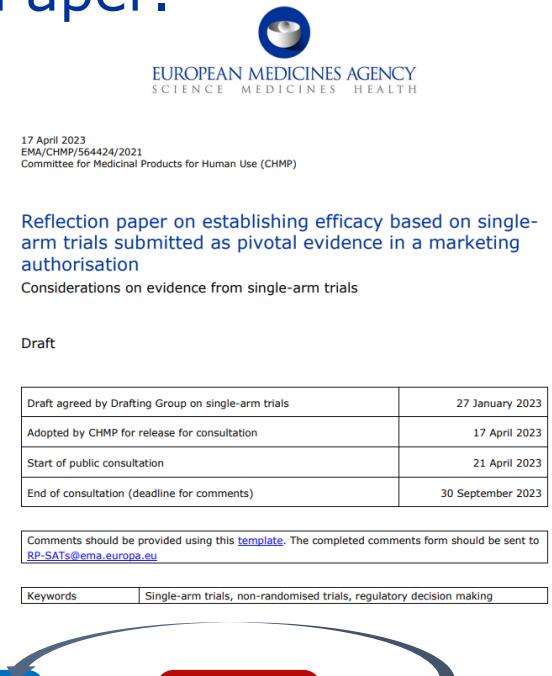
Clarifying the Single Arm Trial Reflection Paper.

In scope

- Methodological considerations specific for SATs across all therapeutic areas

- SATs as pivotal evidence
  - But also important for SATs in early decision making.

- **SAT by design self-standing: Primary research question in the protocol aimed to be answered without integration of control data.**



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17 April 2023
EMA/CHMP/564424/2021
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation

Considerations on evidence from single-arm trials

Draft

Draft agreed by Drafting Group on single-arm trials	27 January 2023
Adopted by CHMP for release for consultation	17 April 2023
Start of public consultation	21 April 2023
End of consultation (deadline for comments)	30 September 2023

Comments should be provided using this template. The completed comments form should be sent to RP-SATs@ema.europa.eu

Keywords	Single-arm trials, non-randomised trials, regulatory decision making

SATs and how close can we get: Causality & treatment effect.

Isolation of treatment effect in SATs

Observed individual outcome on EP can never occur without active treatment **in any** patient

- If #outcome >0 → Treatment effect causally demonstrated

Strongly relies on:

- Knowledge of clinical context
- Choice of endpoint
- Only exceptionally possible perfectly

In practice: Individual outcomes must not be subject to (too much……)

- Bias, variability, measurements errors, flaws in study conduct
- In general, cannot be established without residual uncertainty

Treatment effect estimate

- Contrast to 'no effect' (e.g. 0%) as counterfactual
- Estimate impacted by patient selection
- Endpoint that "isolates" vs most clinically meaningful endpoint

Clarifying the Single Arm Trial Reflection Paper.

For SATs submitted as pivotal evidence, assessment follows standards as for confirmatory setting (ICH E9).

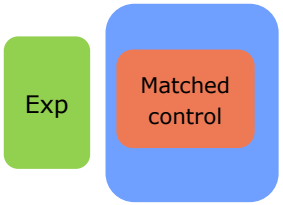
- Importance of pre-specification
  - More pronounced since no randomisation, no blinding.
  - Trial success criterion.

- Adherence to study protocol and SAP post trial initiation critical
  - Unplanned IA
  - Changes to sample size, endpoints, eligibility criteria, etc.

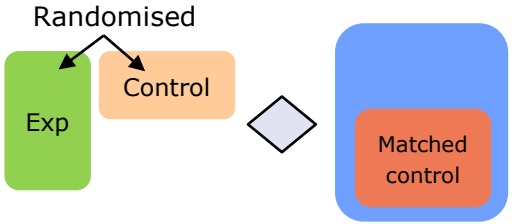
- Variability in natural disease course & thresholds potentially underestimated.

Widening the design space for clinical trials (research)

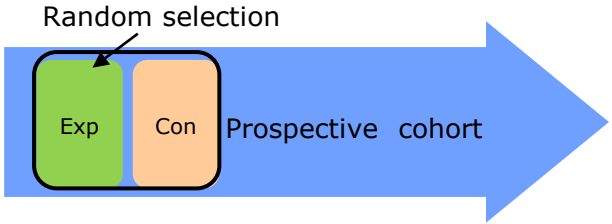
Prospective designs



Non-randomised control



Hybrid designs



Trials Within Cohorts

DOI: 10.1002/pst.2120

MAIN PAPER

WILEY

The use of external controls: To what extent can it currently be recommended?

Hans Ulrich Burger[1] | Christoph Gerlinger[2] | Chris Harbron[3] | Armin Koch[4] | Martin Posch[5] | Justine Rochon[6] | Anja Schiel[7]

Cancer Trials and Design Principles 4

Leveraging external data in the design and analysis of clinical trials in neuro-oncology

Rifaquat Rahman, Steffen Ventz, Jon McDunn, Bill Louv, Irmarie Reyes-Rivera, Mei-Yin C Polley, Fahar Merchant, Lauren E Abrey, Joshua E Allen, Laura K Aguilar, Estuardo Aguilar-Cordova, David Arons, Kirk Tanner, Stephen Bagley, Mustafa Khasraw, Timothy Cloughesy, Patrick Y Wen, Brian M Alexander*, Lorenzo Trippa*

Integration of external control data, with patient-level information, in clinical trials has the potential to accelerate the

Lancet Oncol 2021; 22: e456–65

Kessels et al.
BMC Medical Research Methodology (2023) 23:117
https://doi.org/10.1186/s12874-023-01941-5

BMC Medical Research Methodology

RESEARCH Open Access

The Trial within Cohorts (TwiCs) study design in oncology: experience and methodological reflections

Rob Kessels[1], Anne M. May[2*], Miriam Koopman[3] and Kit C. B. Roes[4]

Complex (platform,…) trial designs

TWICs are an example of a platform (trial) design.

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Patients with Rare Cancers in the Drug Rediscovery Protocol (DRUP) Benefit from Genomics-Guided Treatment

Louisa R. Hoes[1,2], Jade M. van Berge Henegouwen[2,3], Hanneke van der Wijngaart[2,4], Laurien J. Zeverijn[1,2],

- Shared vision: advantages and potential to "personalize" and accelerate drug development, especially in (ultra) rare diseases (EMA concept paper EMA, FDA draft guidance on master protocols).

- May provide opportunity for randomisation in more challenging situations.

- May contain several innovative elements – requiring fundamental consideration for regulatory asssessment.

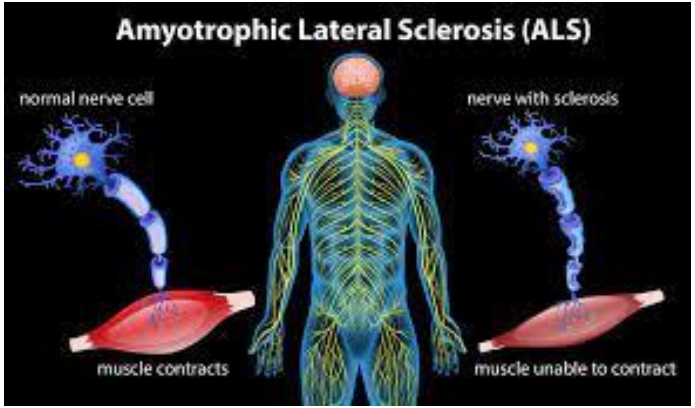
Example: Amyotrophic Lateral Sclerosis

Deadly and severely disabilitating condition.

Apart from riluzole (and edaravone), finding effective treatments very challenging.

About 500 new patients per year (NL)

Good patient registries (NL + EU) with outcome data (ALSFRS, survival,..)



ARTICLE

Hybrid Controlled Clinical Trials Using Concurrent Registries in Amyotrophic Lateral Sclerosis: A Feasibility Study

Ruben P. A. van Eijk[1,2,*], Leonard H. van den Berg[2], Kit C. B. Roes[3], Lu Tian[1], Tze L. Lai[1], Lorene M. Nelson[4], Chenyu Li[1], Anna Scowcroft[5], Jesus Garcia-Segovia[5] and Ying Lu[1,4,*]

CPT 2023

Evaluate feasibility hybrid designs: RCT & registry

A completed randomised, placebo-controlled clinical trial to determine the safety and efficacy of *lithium carbonate* for the treatment of ALS.

- Diagnosis of ALS; an onset of symptoms of at least 6 months and no longer than 36 months prior to inclusion, and a sitting forced vital capacity (FVC) of at least 70%.
- Primary endpoint survival: time to death, tracheostomy or non-invasive ventilation for more than 16 hours per day.
- *Sequential design* to detect a hypothesized hazard ratio (HR) of 0·56
- Stopped for futility when 61 of the 133 (66 L + 67 C) patients reached the primary endpoint

Evaluate feasibility hybrid designs: RCT & registry

Prospective, population-based registry

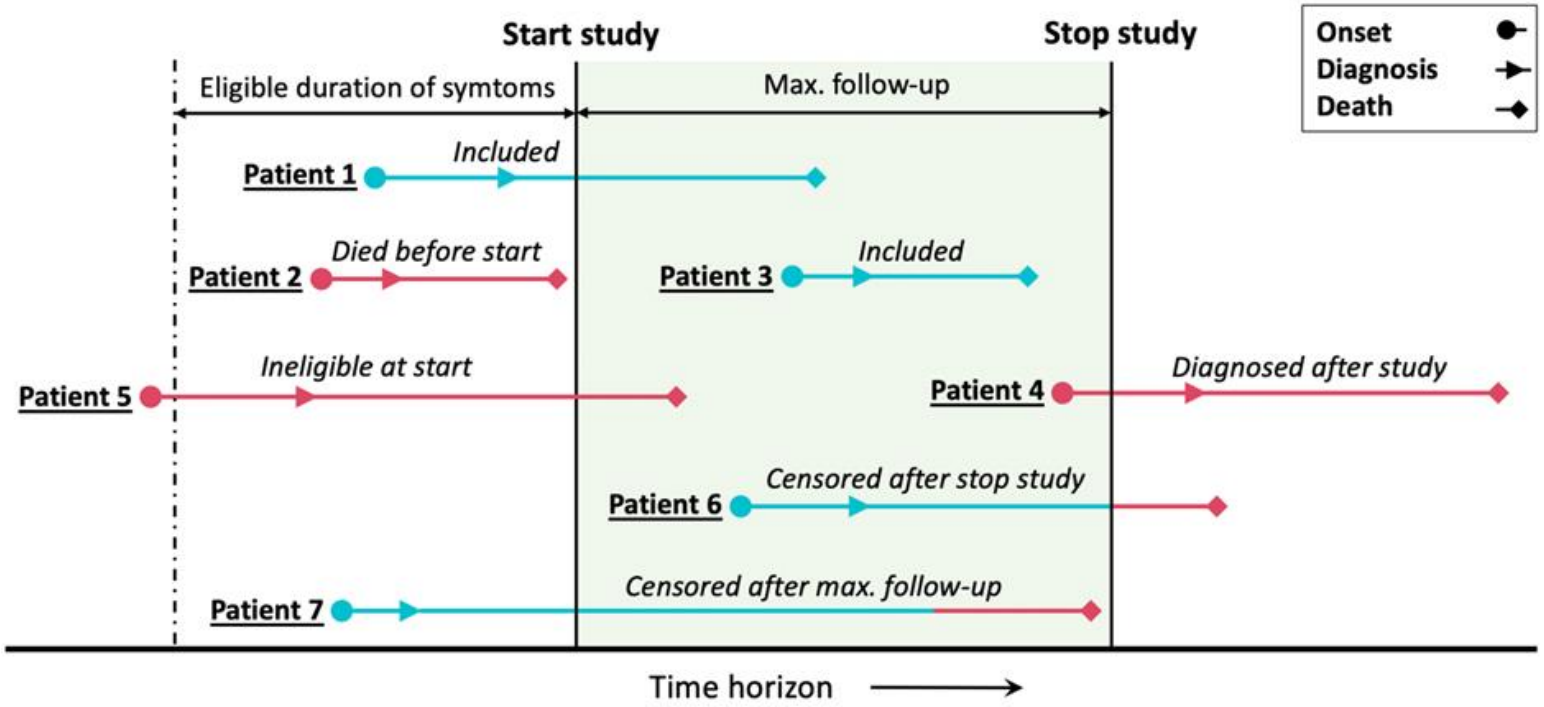
Initiated in April 2006

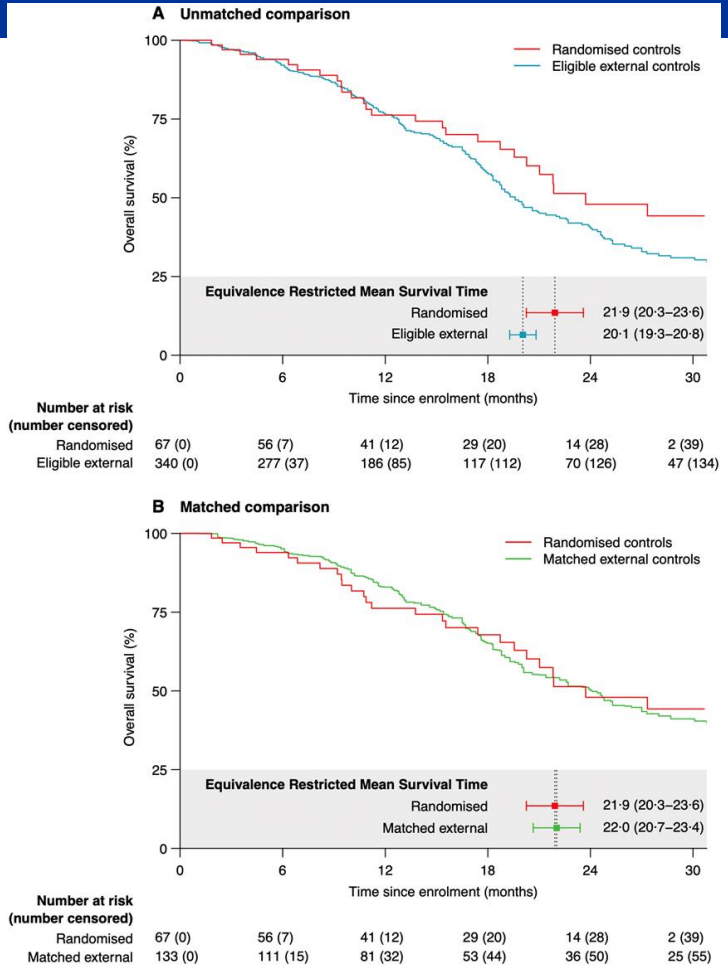
Recruited patients from the same source population as the clinical trial

All patients with ALS are registered centrally at The Netherlands ALS Centre (coverage rate of 80–90%).

Patient characteristics at the day of diagnosis and complete mortality data.

From eligible patients in the registry….(340).



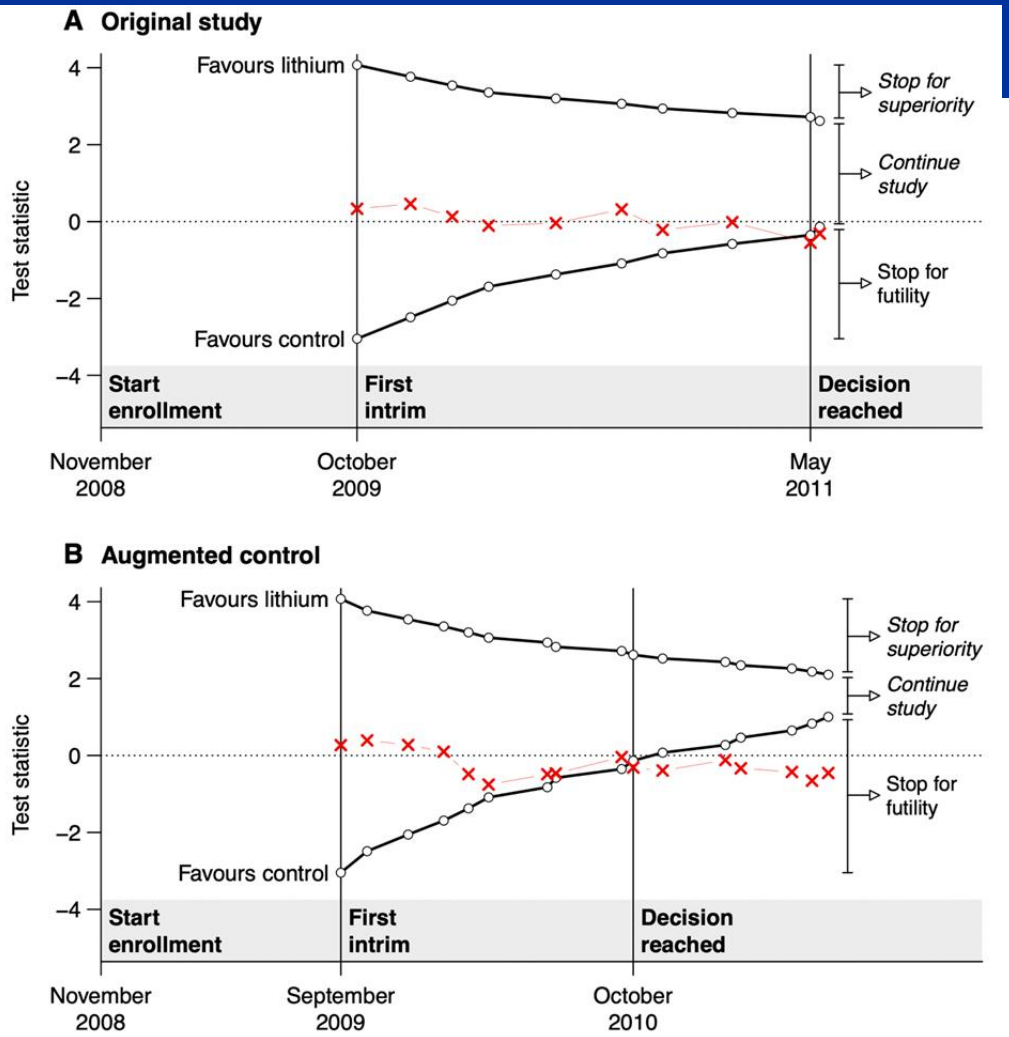


To 133 matched external controls….

Propensity score matching

With equivalence criterion

Check on resulting survival distribution



Potential gain..

Near identical effect size.

A 17·4% reduction in the confidence interval width (estimated HR was 1·11; 95% CI: 0·72-1·71).

Suggestions to further progress.

- Randomisation to extent possible more important than powered for 5% significance.
- Prospective designs including adequate control group vital – for treatments to reach patients (HTA).
- Distinguish “high level of scientific rigor” from the level of measurable uncertainty (e.g., size of T1E).

DOI: 10.1002/pst.2120

MAIN PAPER

WILEY

The use of external controls: To what extent can it currently be recommended?

Hans Ulrich Burger[1] | Christoph Gerlinger[2] | Chris Harbron[3] | Armin Koch[4] | Martin Posch[5] | Justine Rochon[6] | Anja Schiel[7]

“A critical factor …. will be to maintain the same high level of scientific rigor associated with RCTs ….”

Suggestions to further progress.

Prospective high quality registries/cohorts high value for many design options.

Scientific rigor……versus widening the design space

- Work towards framework / criteria for relative assessment of credibility and uncertainty of more complex, innovative designs.

Regulatory interaction in case of (ultra) rare diseases and (almost) no treatments.

- Open and early discussion on alternative designs (of the clinical program) versus general accaptability of specific proposals.