

NEW METHODS FOR PROSPECTIVE STUDIES INVOLVING CHILDREN

Patient Expert Group (PEG) meeting for paediatric patients

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INNOVATIVE DESIGNS IN PAEDIATRICS

In this session we want to look at some applications of innovative designs in paediatrics

- ▶ Adaptive designs
- ▶ Non-randomized studies (“real world data”)
- ▶ Combining randomized controlled trials with real world data

THE PARADIGMS TRIAL

- ▶ Yesterday we learnt about the PARADIGMS trial. Today it serves as an example for an adaptive design.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

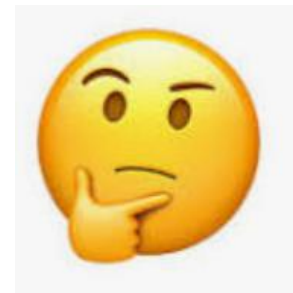
Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis

Tanuja Chitnis, M.D., Douglas L. Arnold, M.D., Brenda Banwell, M.D.,
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for the PARADIGMS Study Group*

- ▶ The publication of the trial results can be found here
<https://www.nejm.org/doi/pdf/10.1056/NEJMoa1800149>

THE PARADIGMS TRIAL

- ▷ **Recap** (structured using PICOS)
- ▷ **Population:** Patients 10 to 17 years of age with relapsing multiple sclerosis
- ▷ **Intervention:** Fingolimod (a new drug at the time)
- ▷ **Control:** Interferon Beta-1a (a drug that is around for longer already and was considered a standard treatment)
- ▷ **Outcome:** annualized relapse rate (number of relapses per year)
- ▷ **Study design:** randomized controlled trial
- ▷ Randomization ... do you remember the idea?



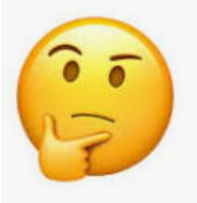
THE SIZE OF THE PARADIGMS TRIAL

- ▶ As mentioned yesterday, the **PARADIGMS trial**
 - ▶ included 190 patients (over 3 years)
 - ▶ who were treated and followed (meaning data were collected) for up to 2 years each
- ▶ The “**size**” of the trial here includes two different aspects
 - ▶ Number of patients
 - ▶ Length of treatment or follow-up
- ▶ **The larger the number of patients and the longer the treatment / follow-up the more informative the trial is.** More informative means the effect of the treatment can be determined with higher precision and the results are more reliable.

THE ORIGINAL PLAN AND ITS ADAPTATION

- ▶ In PARADIMGS, the **original plan** was to randomize 190 patients and follow them up for 2 years each.
- ▶ In the planning of the trial we need to make some assumptions to calculate the required size of the trial.
- ▶ These assumptions might be write or wrong.
- ▶ In **adaptive designs** we can check these assumptions using the data from the trial as they occur.
- ▶ In PARADIGMS, some assumptions regarding the annualized relapse rate (ARR) were made.
- ▶ It turned out that the ARR in PARADIGMS was higher than originally thought. Therefore, the **trial could be stopped early** (providing the required information).

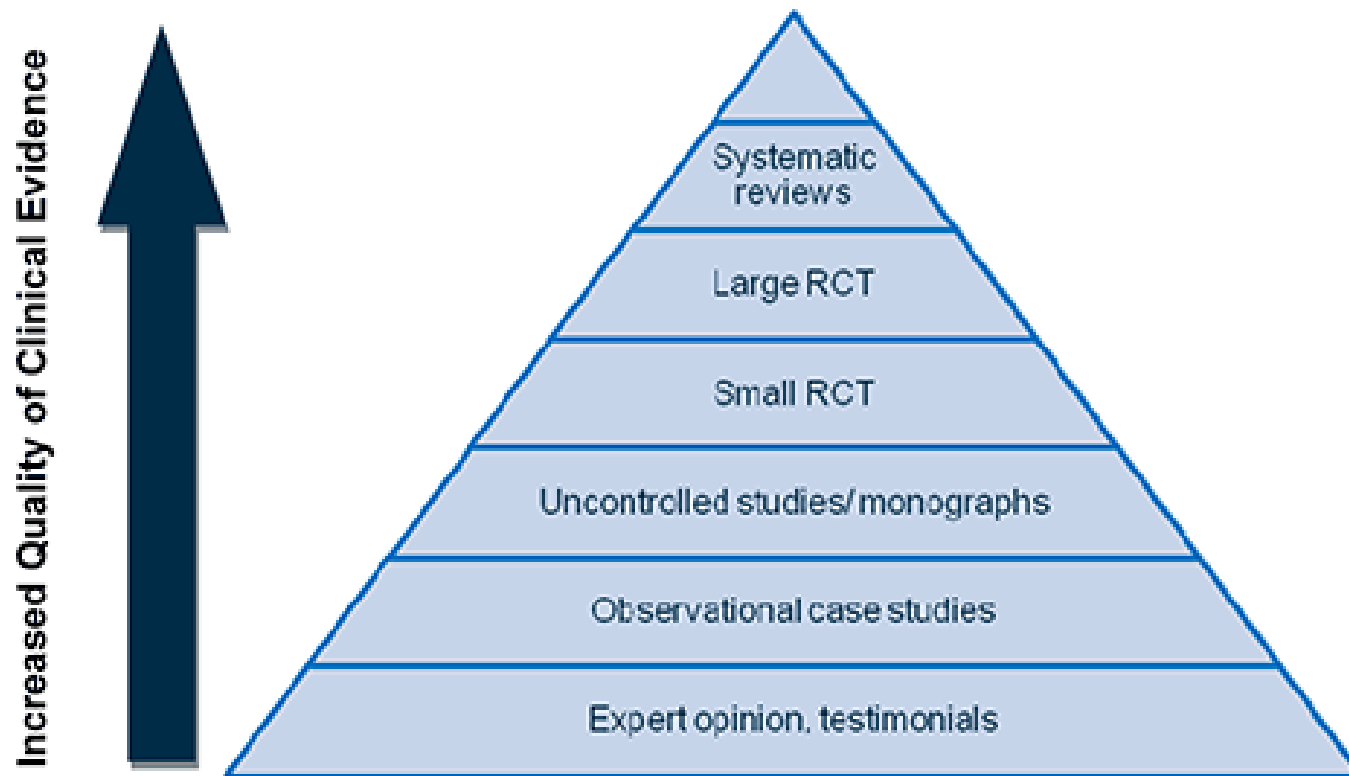
OBSERVATIONAL DATA

- ▶ Not always when we want to compare treatments we can conduct randomized controlled trials.
 - ▶ Can you think of some reasons? 
- ▶ Then we have to rely on **observational data** including clinical registries or electronic health records (eHR); nowadays also referred to as real world data (RWD).
- ▶ The analysis of observational (non-randomized) data is more complicated than the analysis of randomized controlled trials, since the groups might not be directly comparable due to differences in demographic (e.g. age, sex) or clinical (e.g. disease severity) characteristics.

ANALYSIS OF OBSERVATIONAL STUDIES

- ▶ **Statistical techniques** such as propensity scores (modelling the probability to receive a certain treatment) can be used to create balanced patient groups for treatment comparisons.
- ▶ Very recently I supported the analysis of a study in **paediatric cardiology**
 - ▶ 61 children with a severe heart disease who were hospitalized for heart failure or consideration of a certain type of heart surgery from 23 European and North American centers (30 received a new drug in addition to standard of care and 31 received standard of care only)
 - ▶ The new drug was associated with a reduction in deaths, cardiac transplantations and cardiac surgeries

HIERARCHY OF EVIDENCE



- ▷ From <https://www.tga.gov.au/book/scientific-indications-what-evidence-do-you-need-support-your-scientific-indication>

OBSERVATIONAL DATA TO SUPPORT SMALL RANDOMIZED CONTROLLED TRIALS

- ▶ As seen in the evidence pyramid, data from **randomized controlled trials (RCT)** are usually considered to be more **reliable** than observational data
- ▶ However, sometimes it is very hard to run a RCT
- ▶ At the same time observational data might be available
- ▶ Why not combine data from a RCT with observational data?
- ▶ We might want to place **more weight on the (more reliable) data of the RCT** but allow the observational data to support the RCT (“**borrowing**”)
- ▶ The weights might be **dynamic** giving more weight to the observational data the more similar they are to the RCT

EXAMPLE: EARLY PRO-TECT

www.kidney-international.org

clinical trial

A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome



see commentary on page 1104

OPEN

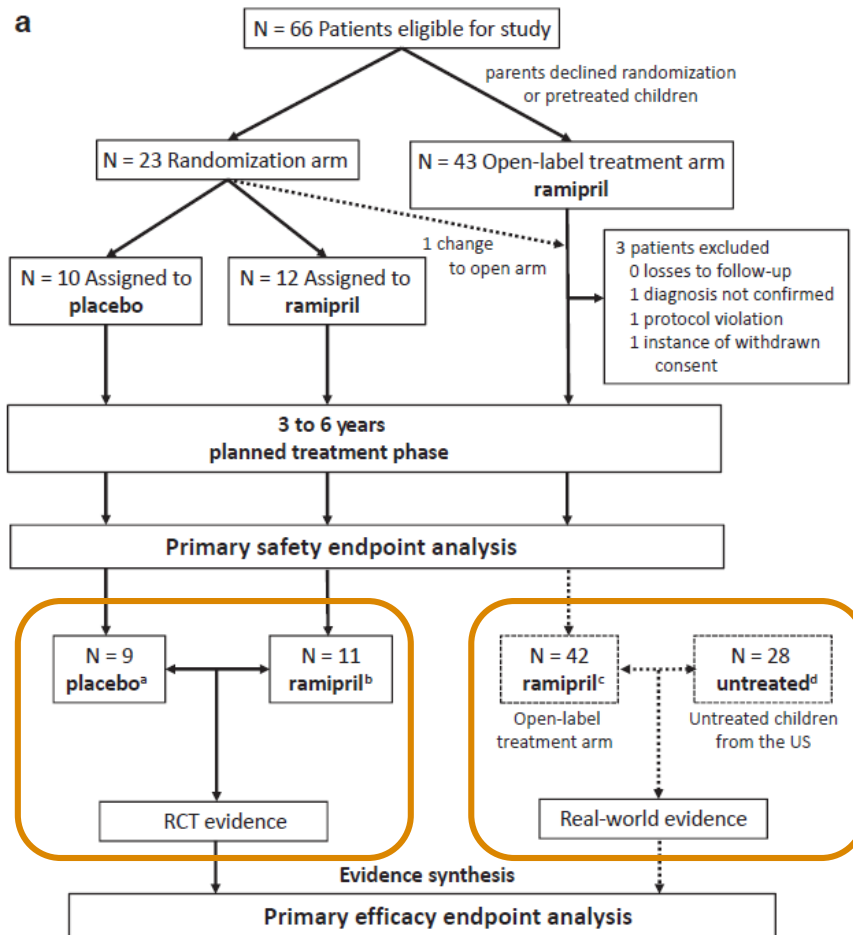
Oliver Gross¹, Burkhard Tönshoff², Lutz T. Weber³, Lars Pape⁴, Kay Latta⁵, Henry Fehrenbach⁶, Baerbel Lange-Sperandio⁷, Hildegard Zappel⁸, Peter Hoyer⁹, Hagen Staude¹⁰, Sabine König¹¹, Ulrike John¹², Jutta Gellermann¹³, Bernd Hoppe¹⁴, Matthias Galiano¹⁵, Britta Hoecker², Rasmus Ehren³, Christian Lerch⁴, Clifford E. Kashtan¹⁶, Markus Harden¹⁷, Jan Boeckhaus¹ and Tim Friede¹⁷; for the German Pediatric Nephrology (GPN) Study Group and EARLY PRO-TECT Alport Investigators^{18,19}

THE EARLY PRO-TECT TRIAL

Briefly summarized using PICOS

- ▶ **Population:** Children with Alport's syndrome, a rare disease leading to kidney failure
- ▶ **Intervention:** Ramipril
- ▶ **Control:** Placebo
- ▶ **Outcome:** Progression to a more severe disease state
- ▶ **Study design:** randomized controlled trial supplemented by real world data (RWD)

EXAMPLE: EARLY PRO-TECT TRIAL



▷ **Randomised controlled trial in children with Alport's syndrome** (rare genetic disorder leading to end-stage kidney disease)

▷ **Observational data**

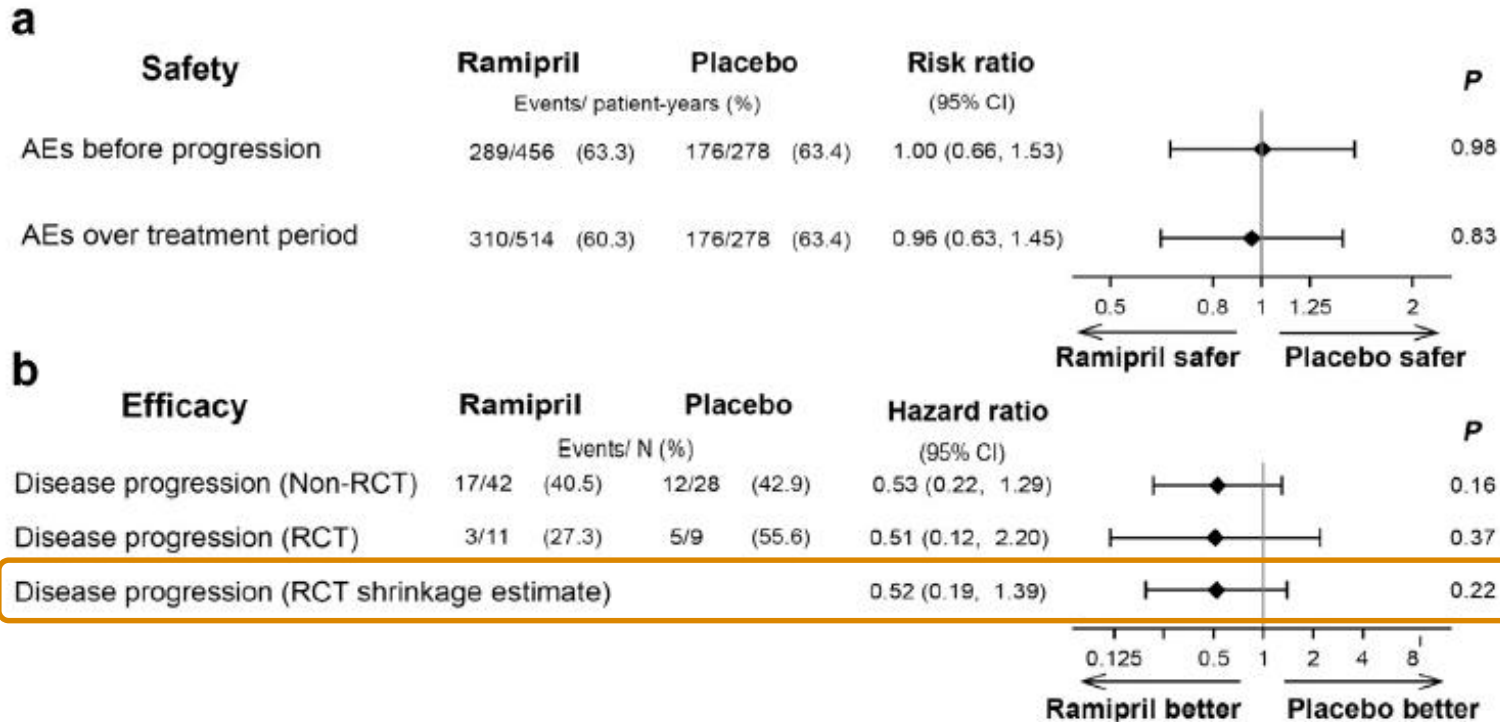
▷ Open-label treatment arm

▷ Natural disease cohort (registry)

Figure 1 in Gross et al (2020) Kidney International

EXAMPLE: EARLY PRO-TECT TRIAL

▷ Figure 2 in Gross et al (2020) *Kidney International*



▷ **Increased precision in estimating the treatment effect:**
 Interval shortened by 42%; equivalent to raising the sample size of the RCT from 20 to 43; i.e. 70 patients in RWE count as 23 RCT patients

KEY MESSAGES

- ▶ **In this session we looked at some innovative designs in paediatrics**
 - ▶ Adaptive designs (PARADIGMS)
 - ▶ Non-randomized studies (“real world data”) (heart failure)
 - ▶ Combining randomized controlled trials with real world data (EARLY PRO-TECT)
- ▶ **These methods help to make clinical research in very rare diseases more efficient leading to faster clinical developments of new treatments.**

