CHALLENGES OF RCT

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

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Pittfalls in clinical trials (bias in RCT)

- Abuse of placebo
- Inappropriate comparators
- Non-inferiority design
- Surrogate end-points
- Fragile populations disregarded/underrepresented
- Adverse reactions overlooked/underestimated
- Selective publications and reporting

Where should we go?
Independent trials

- Education
  - Participation in the preparation of protocols
  - Adequate training of clinical investigators in RCT
- Relevance for patients and public health
  - Comparative effectiveness
  - Patient-centered outcomes
  - Validation of commercial trial data
- Transparency
  - Registration of protocols
  - Access and sharing of participants' data
  - Committment to publish
- Ownership of data till publication

The fund for independent research at AIFA

(Art. 48, law 326/2003)

- Promotion of independent research is among the missions of AIFA
- Pharmaceutical companies are obliged to devote 5% of their promotional expenditure to a fund for independent research

The call for proposals

AREA 1

Orphan drugs for rare diseases and drugs for non-responders

AREA 2

Comparison among drugs and therapeutic strategies

AREA 3

Strategies to improve the appropriateness of drug use and pharmacoepidemiology studies

TO ESTABLISH THE TOPICS OF THE YEARLY CALL HEARINGS OF SCIENTIFIC SOCIETIES AND STAKEHOLDERS ARE MADE.

A WEB SITE IS AVAILABLE TO COLLECT SUGGESTIONS

	2006	2007	2008	2009
LETTERS OF INTENT	402	454	360	302
SELECTED PROJECTS	101	99	106	61
FUNDED PROJECTS	54	51	46	38

EXAMPLES OF APPROVED PROJECTS

First adjuvant trial on all aromatase inhibitors in early breast cancer. A phase 3 study comparing anastrozole, letrozole and exemestane, upfront or sequentially.

A randomized clinical trial of trastuzumab optimization in patients with locally advanced and/or metastatic breast cancer overexpressing HER-2 after a first-line chemotherapy plus trastuzumab.

Multicentre randomized controlled study of azathioprine versus interferon-beta in relapsing-remitting multiple sclerosis.

EXAMPLES OF APPROVED PROJECTS

A randomized placebo-controlled study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins.

A randomized prospective multicentre trial to compare the effect on chronic allograft nephropathy of mycophenolate mofetil versus azathioprine as the sole immunosuppressive therapy for kidney transplant recipients.

A randomized controlled trial to evaluate the efficacy of low molecular weight heparin on pregnancy outcome of women with previous pregnancy complications.

Ecrin Eligibility Criteria

(Lack of adherence to the eligibility criteria implies rejection)

1. Multicentre trial run in at least two European countries.

2. Rules for transparency:

- Commitment to register the trial in a public register (for example on EudraCT or Clinicaltrials.gov) before inclusion of the first participant
- Commitment to post trial results in a public register (for example on EudraCT or Clinicaltrials.gov) one year after the trial is completed, i.e. last follow up of the last patient for the primary outcome.
- Commitment to publish results irrespective of findings.
- Commitment to make raw anonymised data sets available to the scientific community upon request.
- Declaration of conflicts of interest.

3. Commitment to fairly describe the contribution of ECRIN and its national partners in the publications.

Ecrin evaluation Criteria

(basis for the ECRIN Scientific Board assessment)

1. Rationale for the trial - including the choice of the experimental intervention and the comparator - based on extensive and up-to-date review and analysis of relevant clinical and preclinical data.

2. Suitable overall trial design appropriate to the clinical question.

3. Clinical relevance for patients and public health.

Regulatory confidentiality

The reasons for transparency

- The industry is not the sole financer of research.
- Clinical trials require the participation of patients, who take part free of charge.
- In most European states the drug market is prosperous because it is guaranteed by national health services.
- Secrecy may be justifiable in connection with information regarding the production of the active principles and the methods utilized for drug discovery.
- But information on drug development including pre-clinical findings and clinical controlled trials must be available for scrutiny by clinicians and patients.

CHANGE NEEDED IN EUROPEAN LEGISLATION

- QUALITY, EFFICACY, SAFETY
- QUALITY, EFFICACY, SAFETY AND THERAPEUTIC ADDED VALUE

Two pivotal trials needed to support MAA

One sponsor-driven RCT	One independent RCT

FUTURE CHALLENGES OF RCT

- POLYPHATOLOGY → DE-PRESCRIBING
- GENOMICS → PERSONALIZED TRIALS