GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

OVERVIEW OF DRUG DEVELOPMENT AND TYPES OF CLINICAL TRIALS

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DISCLOSURES

- Denis Lacombe has reported no conflict of interest
- Ian Tannock has reported no conflict of interest
- Anita Margulies has reported no conflict of interest
- Jan Bogaerts has reported no conflict of interest
- Christian Dittrich has reported no conflict of interest

KEY POINTS

- Drug development follows a structured sequence of different steps ensuring safety and aiming at therapeutic progress
- The process is structured by the successive conduct of phase I, II, and III clinical trials
- Appropriate interpretation of clinical trial results is paramount
- The forms and the methods of drug development are evolving in the era of targeted agents

DEFINITIONS (I)

- A clinical trial is a research study conducted in patients, with patients and for patients, to answer specific questions about their treatment, diagnosis or follow-up

- Clinical trials (also called interventional studies) are used to determine whether new biomedical or behavioral interventions are both safe for patients and effective at treating their disease
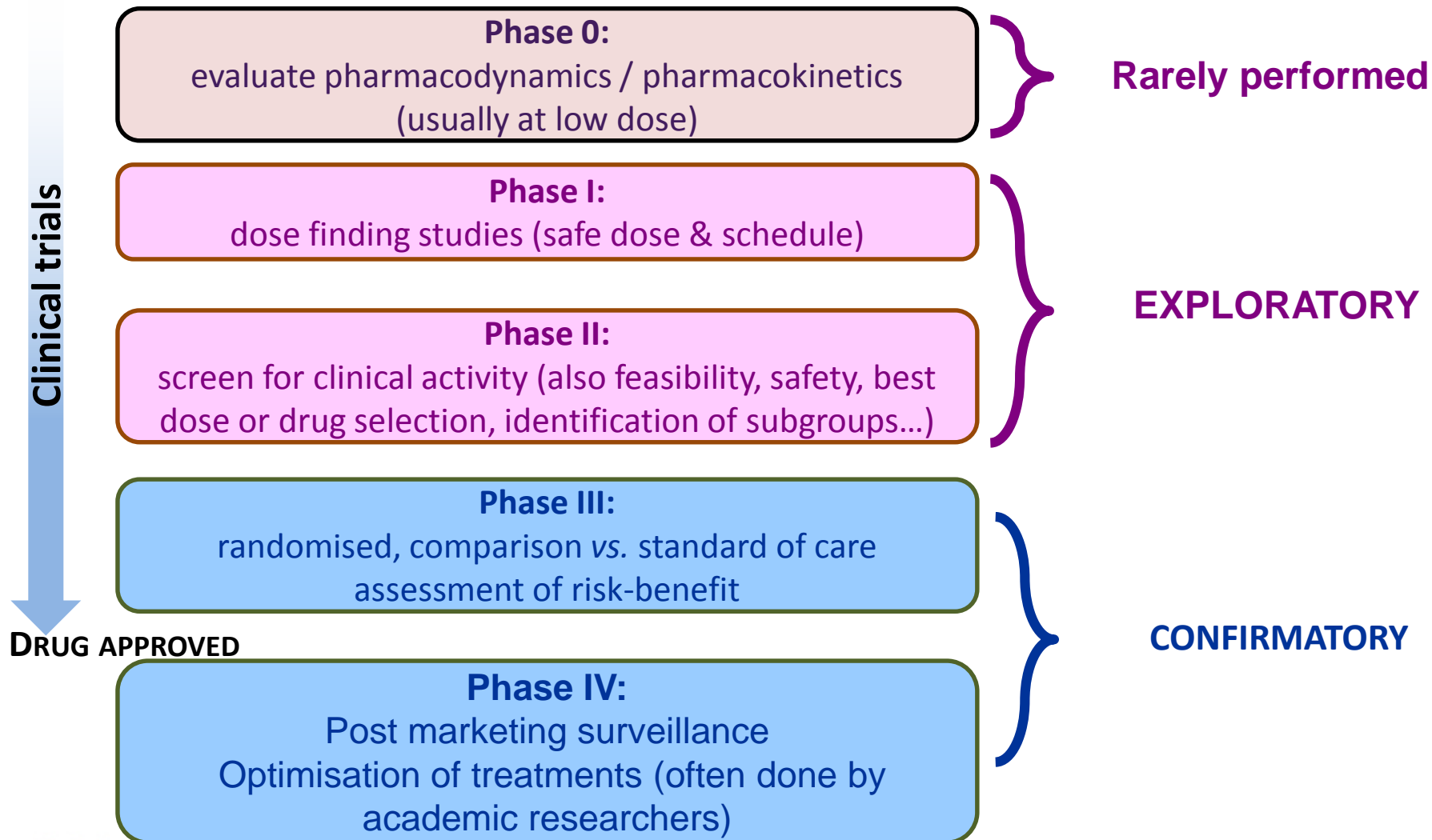
(National Institutes of Health's (NIH) Definition http://grants.nih.gov/grants/glossary.htm#C)

DEFINITIONS (II)

- Non-interventional clinical study: A study where medicinal product(s) if given, are prescribed as per current practice. The objectives may be to collect additional data relating to the disease or its treatment such as cognitive function, long term toxicity profile…

- **drug development process.** A generic term for the process by which an investigational drug advances from preclinical studies to clinical trials, through to approval for marketing after review by regulatory agencies.

STEPS IN CLINICAL DEVELOPMENT PROGRAMME

Clinical trials

Phase 0:
evaluate pharmacodynamics / pharmacokinetics
(usually at low dose)

Rarely performed

Phase I:
dose finding studies (safe dose & schedule)

Phase II:
screen for clinical activity (also feasibility, safety, best
dose or drug selection, identification of subgroups...)

EXPLORATORY

Phase III:
randomised, comparison *vs.* standard of care
assessment of risk-benefit

DRUG APPROVED

Phase IV:
Post marketing surveillance
Optimisation of treatments (often done by
academic researchers)

CONFIRMATORY

PHASE I

- ## Primary objectives of phase I
  - Identify the optimal recommended phase II dose (RP2D)
    Assess the safety profile and the risk for dose-limiting toxicities (DLTs)
  - Pharmacokinetics, PK/PD

- ## Dose-limiting toxicity (DLT) as the main safety endpoint
  - Toxicity that is considered unacceptable due to severity and/or irreversibility and limits further dose administration

- ## Phase I in the new era of Molecular Targeted Agents:
  - Chronic and mechanism based toxicity (longer safety monitoring)
  - Assessment of the early and late toxicity profile
  - Translational research/ drug activity

EXAMPLES OF DESIGNS FOR PHASE I

- Classical model «3+3»: including patients by block of 3 per dose level to document DLTs
  - MTD defined when 2/6 patients experience DLTs
- Continuous reassessment method:
  - Fit a model of the dose-toxicity curve on all the previously documented toxicity.
  - Optimise patients to be treated at a potentially active dose
- Phase I targeted agents/ chronic toxicities
  - Potentially designed based on a dual end-point: toxicity and activity
  - More likely to include a translational research end-point.

PHASE II

- To identify biological anti-tumour activity, to get better understanding of the safety profile

- One or two-stage designs
  - One-stage: simplest design (e.g. A'Hern design)
  - Two-stage allow early stopping if insufficient activity (e.g. Simon design)
  - Combining activity and safety end-points (e.g. Bryant and Day design)

- Single arm or randomised
  - Randomisation is recommended when no historical data, time to event end-points, screening for new treatments, combination

RANDOMISED PHASE II

- Randomised phase II are usually non comparative
  - Control arm is used for benchmarking (contemporary control arm)
- Randomised phase II for **selection**
  - Pick the winner/ drop the loser to further continue with relevant treatment arms in phase III
- Randomised phase II for **screening of different treatments**
  - Can be comparative
  - End-point is usually time to event for early decision

DATA NOT TO BE OVER INTERPRETED
UNDERPOWERED
NOT FOR FINAL CONCLUSION

PHASE III

- Phase III clinical trials compare the new treatment with the current standard of care for that specific disease, or with placebo when applicable, usually In large numbers of patients, to find out whether the new treatment is better.

- In phase III clinical trials patients are usually randomised to receive either the investigational treatment or the standard treatment.

- Phase III usually have a clinically meaningful primary end-point to change practice: overall survival, quality of life, or validated surrogates for fundamental outcome measures.

- Phase III may have a number of secondary end-points;
  - Alternative efficacy end-points
  - Safety endpoints
  - Quality of Life
  - Health economics…

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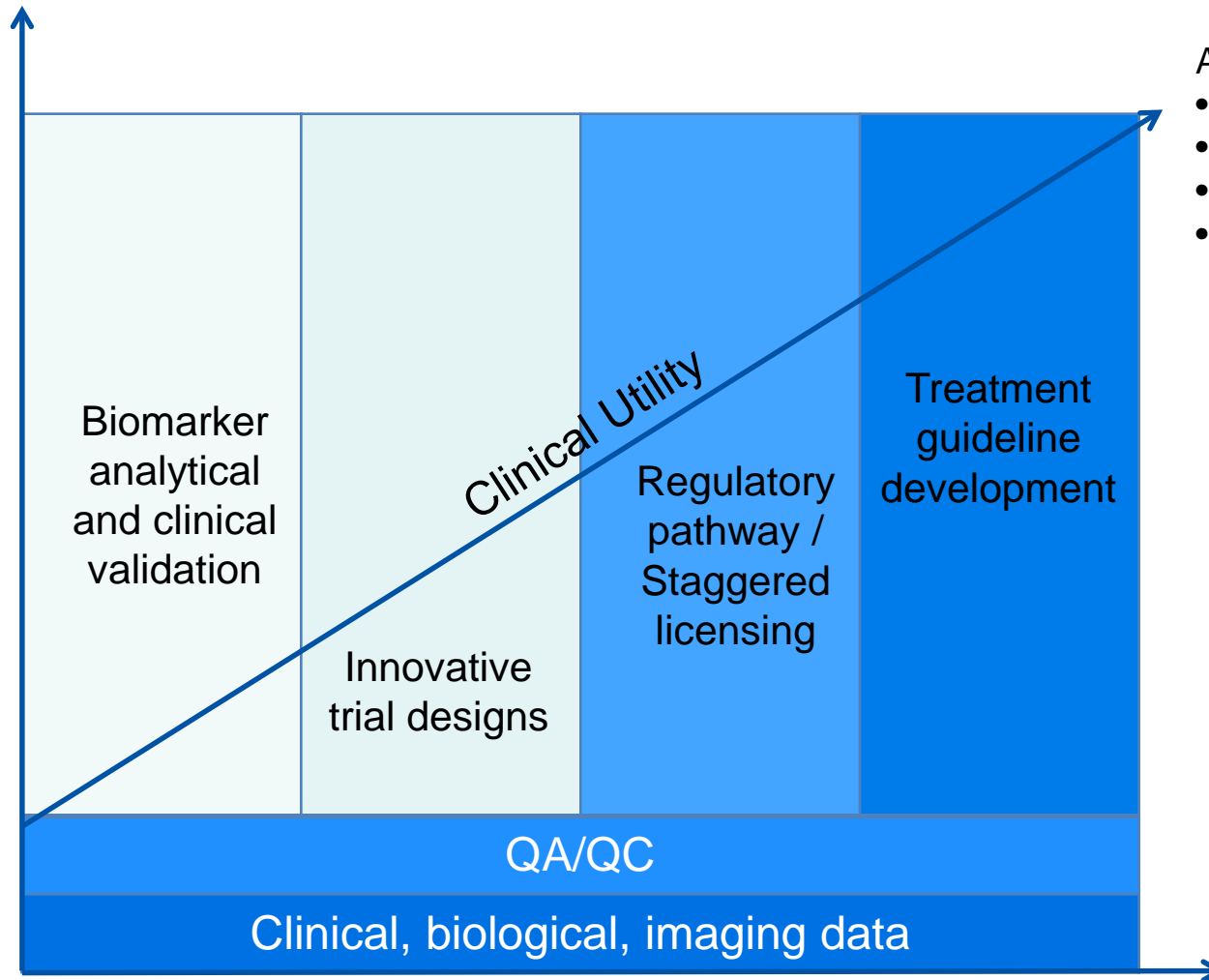
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BIOMARKER / TARGET BASED CLINICAL TRIALS

- **Targeted clinical trials** can be much more efficient than untargeted clinical trials, if we know whom to target
  - Prognostic marker: separate patients according to disease prognosis
  - Predictive marker: identify sets of patients for whom the effect of a treatment varies
  - Targeted (stratified) clinical trial: allocate treatment arms to patients who are marker positive (and/or marker negative)
- **Basket trial**: based on the hypothesis that presence of a molecular marker predicts response to a targeted therapy independent of tumour histology

TOWARDS NEW HEALTHCARE SYSTEMS

Access to effective care:
- Outcome research
- Cost effectiveness
- Health Technology Assessment
- Real life situation

Biomarker analytical and clinical validation

Clinical Utility

Regulatory pathway / Staggered licensing

Treatment guideline development

Innovative trial designs

QA/QC

Clinical, biological, imaging data

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Thank you!