Overview of Drug Development: Adaptive Seamless Design

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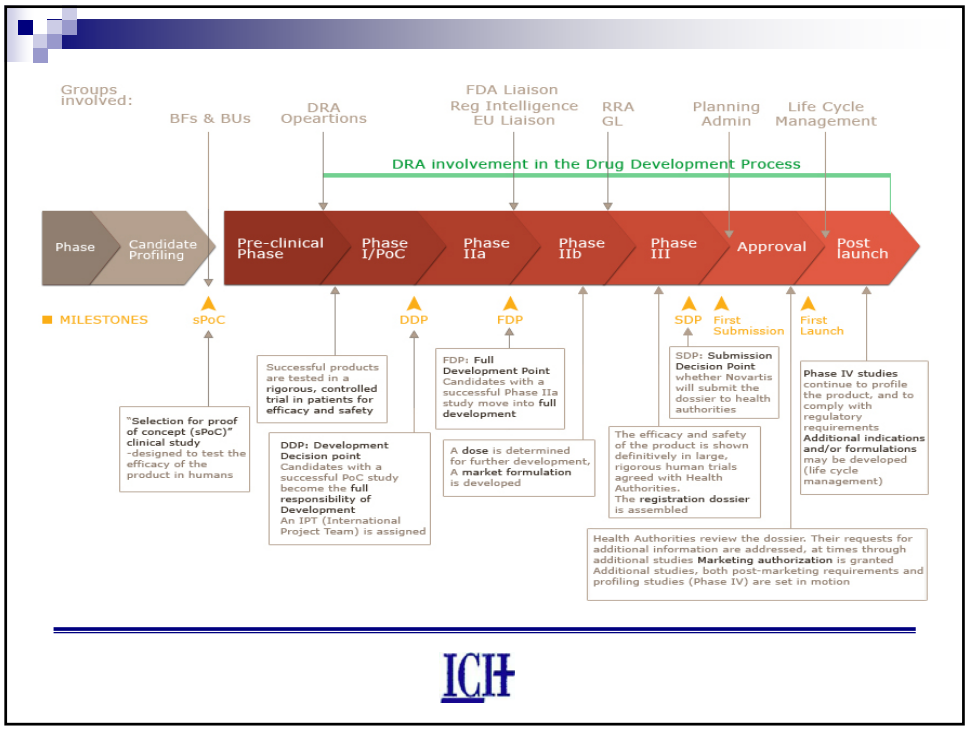

Clinical Trials

Definition	Study types included
Phase I A study that has Tolerability or PK as primary endpoint in the protocol, independently of the study population and of secondary parameters	■ Safety & Tolerability studies (SD or MD in patient or HV) ■ Oncological studies in patients with tolerability / MTD as primary endpoint (efficacy might be a secondary endpoint) ■ Drug-Drug interaction &Food Effect ■ PK in renal or hepatic impaired patients
Phase IIA An exploratory (non-pivotal) study that has as a primary endpoint either clinical efficacy, PD, or biological activity, irrespective of whether conducted in patients or healthy volunteers.	■ Proof of concept, efficacy, or mechanism ■ Mechanistic studies ■ Dose range exploration ■ Pilot studies
Phase IIB A definite dose range finding study in patients with efficacy as primary endpoint. Exceptionally, Phase II studies can be used as pivotal trials (see below), if the drug is intended to treat life-threatening or severely-debilitating illnesses (e.g., in oncological indications)	■ Definite dose finding studies ■ Extension studies of Phase IIB studies

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Clinical Trials

Definition	Study types included
Phase IIIA A study that is a pivotal* trial, e.g., a trial designed and executed to get the statistically significant evidence of efficacy and safety as required by HAs for approval of a NDA or sNDA. This also includes studies with the aim to include claims into the label as well as postmarketing commitments.	■ Pivotal studies (vs placebo or comparator) ■ Long term saftey studies requied for registration ■ Local registration studies ■ Post marketing study commitments ■ Phase III A extension studies
Phase IIIB A study that is started prior to approval and whose primary intention is the support of publications rather than registration or label changes, e.g. results are not intended to be included in the submission dossier.	All studies intended to support publication claims or to prepare launch, which start before approval but are not intended for regulatory submissions
Phase IV A study that is started after approval and whose primary intention is the support of publications rather than registration or label changes, e.g. results are not intended to be included in a submission dossier.	Post marketing surveillance studies Studies intended to support publication claims

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Pivotal Trial

- **A pivotal trial is a trial designed and executed to get the statistically significant evidence on efficacy and long term safety as required by HAs for approval of an NDA or sNDA.**
- **This also includes studies with the aim to include claims into the label.**

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Clinical Development Plan

- **The Clinical Development Plan (CDP) is the tool that "bridges the gap between vision and the day-to-day activities of large multidisciplinary organizations. The vision is transformed into distinct implementation phases and discrete steps, called clinical studies, each with well-defined milestones and deliverables."**

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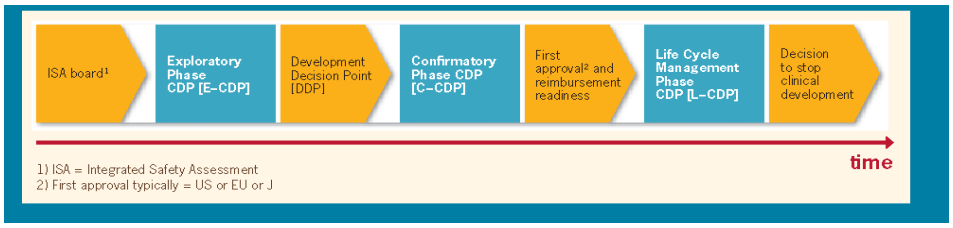
Stages of clinical development Plan



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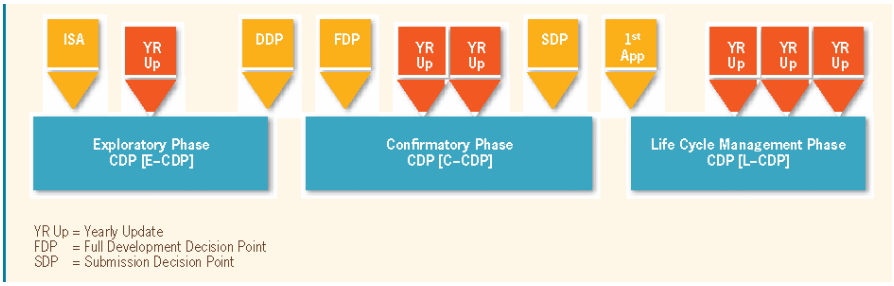
Stages of clinical development Plan



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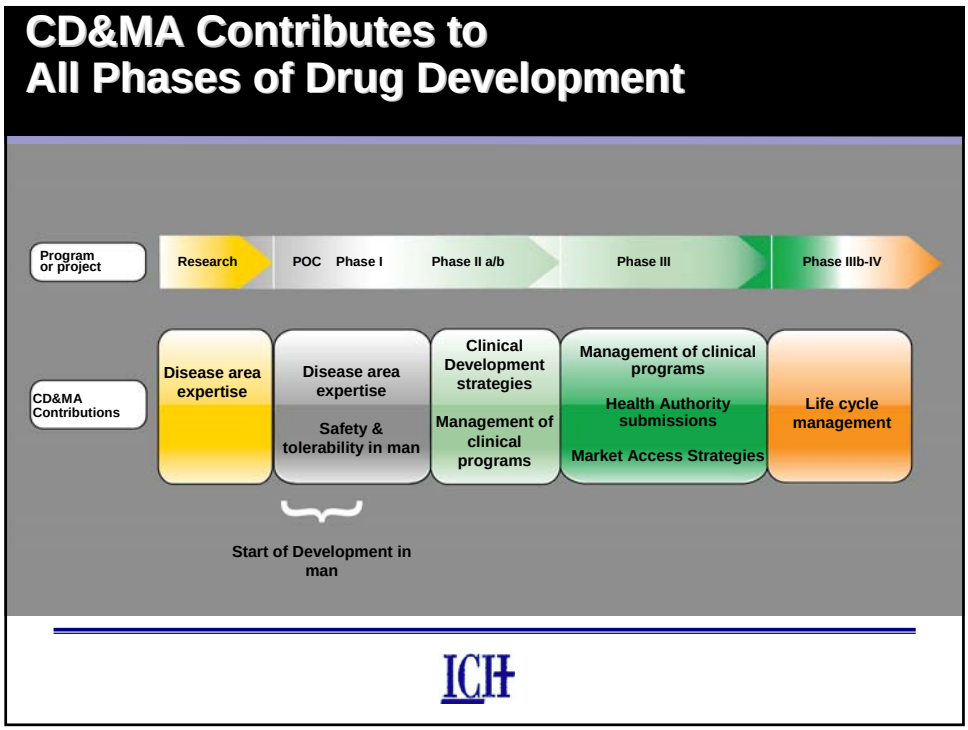
CD&MA Contributes to All Phases of Drug Development
Program or project
Research
POC
Phase I
Phase II a/b
Phase III
Phase IIIb-IV
CD&MA Contributions
Disease area expertise
Disease area expertise
Safety & tolerability in man
Clinical Development strategies
Management of clinical programs
Management of clinical programs
Health Authority submissions
Market Access Strategies
Life cycle management
Start of Development in man
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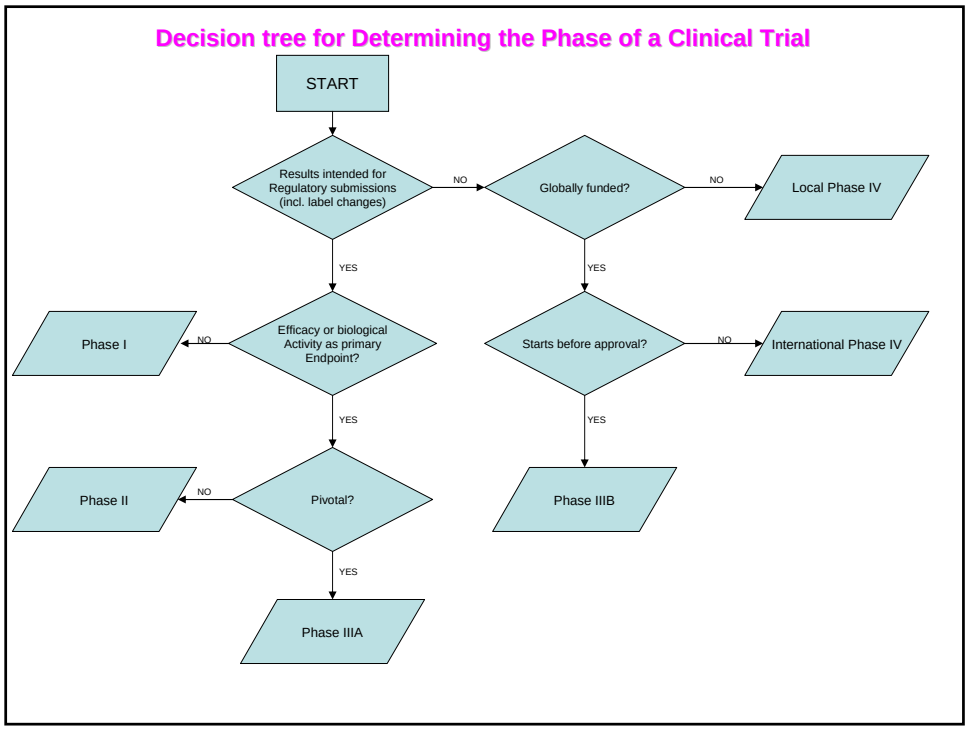
Decision tree for Determining the Phase of a Clinical Trial
START
Results intended for Regulatory submissions (incl. label changes)
NO
Globally funded?
NO
Local Phase IV
YES
YES
Phase I
NO
Efficacy or biological Activity as primary Endpoint?
Starts before approval?
NO
International Phase IV
YES
YES
Phase II
NO
Pivotal?
Phase IIIB
YES
Phase IIIA

Adaptive Designs in Clinical Development

- Introduction and motivation for Adaptive Designs
  - Adaptive and Seamless designs
- Classical vs. Seamless development
- Example of Adaptive Seamless Design
- Final Remarks

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Possible Adaptations

- **Adaptive designs:** using accumulating data to decide on how to modify aspects of the trial without undermining the validity and integrity of the trial

- **Adaptations can include**
  - Early stopping (futility, early rejection)
  - Sample size re-assessment
  - Treatment allocation ratios
  - Treatment arms (dropping, adding arms)
  - Hypotheses (Non-inferiority vs. superiority)
  - Population (inclusion/exclusion criteria; subgroups)
  - Test statistics
  - Combine trials / treatment phases (Adaptive Seamless Designs)

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Classical Full Development

- **Fixed Trial Designs Paradigm, in particular for Phase III**
  - Standard trial designs allow little learning during the conduct of the trial
  - "Established" adaptations are used in group-sequential trials where stopping for superiority or futility can be done according to pre-defined rules at interim analyses
  - Clearly separated development phases (II and III)
  - If applied to all clinical projects one misses opportunities for better use of information and more ethical drug development

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Classical Phase III: Confirmation, Hypothesis Testing and Error Control

- **Proof of efficacy in phase III trials:**
  - Show that observed treatment effect is 'real' and not just random via testing of statistical hypotheses
  - Regulatory practice and guidelines (e.g. ICH E9) ask that the false positive error rate is controlled for pivotal trials (usually 2.5%)
  - Trial designs, analysis and decisions rules at interim analysis are pre-defined
  - Emphasis on trial 'integrity' (e.g., regarding confidentiality of interim results)
- **Error control:**
  - Multiple hypothesis testing or changes of design characteristics at interim alters the false positive error rate of a standard statistical test

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Adaptive /seamless phase II/Phase III trial

Primary objective **- to combine "treatment selection" and "confirmation" in one trial**

- **Enroll patients into the trial**
- **During the trial, select the optimal dose (or population) based on interim data based on surrogate marker, early read-out of endpoint, or primary endpoint**
- **Enrollment continues only on the selected dose and the comparator arm**

All data from chosen arm and comparator is used in final analysis, using novel statistical methods for combining evidence from first and second stage to control of false positive error rate and maintaining trial integrity

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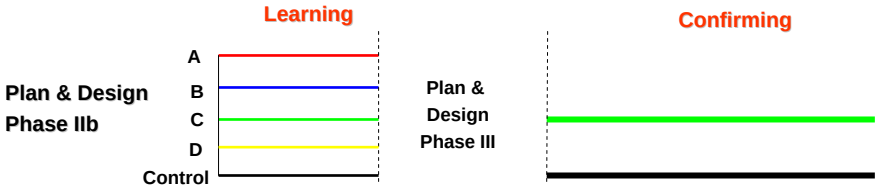
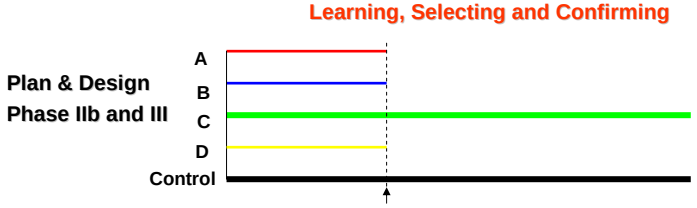
Comparison of ASD for treatment selection with separate phase II and III trials (1)

- **Standard 2 phases**



- **Adaptive Seamless Design**



- **Dose Selection**

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Comparison of ASD for treatment selection with separate phase II and III trials (2)

- **Advantages of adaptive seamless designs**
  - Shorter overall development time → effective drugs are made available earlier for the patients
  - Increase of information value given the same number of patients
  - Long term safety available earlier (extension of Stage I patients)
- **Logistical differences**
  - Number of treatment groups can change during trial → resulting implications in drug supply
  - Centers would have to be made aware of flexible sample sizes
  - Informed consent may need to be modified at interim
  - Sufficient time for Health Authority interaction
  - Careful consideration of trial integrity issues, including the interim analysis decision process and personnel

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RAD001+Femara, advanced breast cancer

- **Motivation for adaptation**

Selection of appropriate patient sub-group and confirmation of benefit in one seamless phase II/III trial

- **Design specifications: 2-stage seamless adaptive design**

Stage 1

- sub-group selection (options: sub-group or all-patients)
- futility decision at two time points
- sub-group considered is defined upfront, based on evidence external to the trial
- Sample size could be adjusted at interim points

Stage 2

- achieve confirmation of treatment benefit while maintaining integrity of trial (false positive rate and bias are controlled)

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RAD001+Femara, advanced breast cancer

- Adaptive trial design was reviewed by FDA and EMEA, and considered acceptable for the trial
- Careful consideration and detail was required for the interim analysis and decision process
  - What data will be needed to decide to adapt?
  - Who will see this data, and make this decision?
  - Will the results of this decision bias the trial?
- Overall, a positive response

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Final Remarks

- Need for making drug development process more efficient is recognized by all parties
- Key value of adapting is not in reducing sample size, but given a constant sample size, increase the information value, thus making adaptive designs more ethical/efficient
- Ethical reasons justify novel adaptive designs, which combine learning and confirmation in one single trial while controlling the overall type I error rate
- Novartis is committed and dedicated to invest in Research & Development of ASD on a global level while being in continuous discussions with Health Authorities

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